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Title:
CYCLIC AMINE DERIVATIVES AND THEIR USE AS DRUGS

Abstract:
A compound represented by general formula (I), a pharmaceutically acceptable acid addition salt thereof or a pharmaceutically acceptable C1-C6 alkyl addition salt thereof, and their medical applications. Since these compounds inhibit the action of chemokines such as MIP-1 alpha and/or MCP-1 on target cells, they may be useful as a therapeutic drug and/or preventative drug in diseases, such as atherosclerosis, rheumatoid arthritis, and the like where blood monocytes and lymphocytes infiltrate into tissues.

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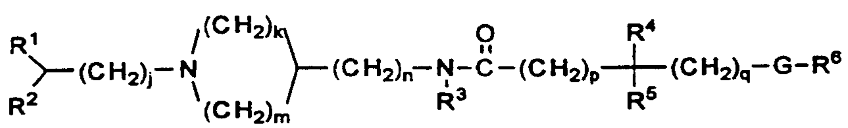

(I)

(57) **Abstract**

A compound represented by general formula (I), a pharmaceutically acceptable acid addition salt thereof or a pharmaceutically acceptable C_1–C_6 alkyl addition salt thereof, and their medical applications. Since these compounds inhibit the action of chemokines such as MIP–1α and/or MCP–1 on target cells, they may be useful as a therapeutic drug and/or preventative drug in diseases, such as atherosclerosis, rheumatoid arthritis, and the like where blood monocytes and lymphocytes infiltrate into tissues.

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SPECIFICATION

Cyclic Amine Derivatives and Their Use as Drugs

Field of the Invention

This invention relates to novel cyclic amine derivatives.

This invention also relates to chemokine receptor antagonists that may be effective as a therapeutic agent and/or preventive agent for diseases such as atherosclerosis, rheumatoid arthritis, psoriasis, asthma, ulcerative colitis, nephritis (nephropathy), multiple sclerosis, pulmonary fibrosis, myocarditis, hepatitis, pancreatitis, sarcoidosis, Crohn's disease, endometriosis, congestive heart failure, viral meningitis, cerebral infarction, neuropathy, Kawasaki disease, and sepsis in which tissue infiltration of blood leukocytes, such as monocytes and lymphocytes, play a major role in the initiation, progression or maintenance of the disease.

Description of related art

Chemokines are a group of inflammatory/immunomodulatory polypeptide factors which have a molecular weight of 6-15 kD and are produced by a variety of cell types, such as macrophages, monocytes, eosinophils, neutrophiles, fibroblasts, vascular endotherial cells, smooth muscle cells, and mast cells, at inflammatory sites. The chemokines can be classified into two major subfamilies, the CXC chemokines (or α-chemokines) and CC chemokines (or β-chemokines), by the common location of the four conserved cysteine residues and by the differences in the chromosomal locations of the genes encoding them. The first two cysteines of CXC chemokines are separated by one amino acid and those of CC chemokines are adjacent. For example IL-8 (abbreviation for interleukin-8) is a CXC chemokine, while the CC chemokines include MIP-1α/β (abbreviation for macrophage inflammatory protein-1α/β), MCP-1 (abbreviation for monocyte chemoattractant protein-1), and RANTES (abbreviation for regulated upon activation, normal T-cell expressed and secreted). There also exist chemokines which do not fall into either chemokine subfamily. They are lymphotactin, which has only two cysteines and defines the C chemokine, and fractalkine that has a chemokine-like domain in the mucin structure in which the first two cysteines are separated by three amino acids and hence defines CX_3C chemokine. These chemokines promote chemotaxis, cell migration, increase the expression of cellular adhesion molecules such as integrins, and cellular adhesion, and are

thought to be the protein factors intimately involved in the adhesion and infiltration of leukocytes into the pathogenic sites in such as inflammatory tissues (for references, see for example, Vaddi, K., et al., The Chemokine Facts Book, Academic Press, 1997; Chemoattractant Ligand and Their Receptors, Horuk, R., Ed., CRC Press, 1996; Ward, G.W., et al., Biochem. J., 1998, 333, 457; Luster, A.D., New Engl. J. Med., 1998, 338, 436; Baggiolini, M., Nature, 1998, 392, 565; Rollins, B.J., Blood, 1997, 90, 909; Alam, R., J. Allergy Clin. Immunol., 1997, 99, 273; Hancock, W.W., Am. J. Pathol., 1996, 148, 681; Taub, D.D., Cytokine & Growth Factor Rev., 1996, 7, 335; Strieter, R.M., et al., J. Immunol., 1996, 156, 3583; Furie, M.B., et al., Am. J. Pathol., 1995, 146, 1287; Schall, T.J., et al., Current Opinion in Immunology, 1994, 6, 865; Edginton, S.M., Biotechnology, 1993, 11, 676).

For example, MIP-1α causes a transient increase in intracellular calcium ion concentration levels and induces migration of T lymphocytes, B lymphocytes (see for example, Taub, D.D., et al., Science, 1993, 260, 355; Schall, T.J., et al., J. Exp. Med., 1993, 177, 1821), and eosinophiles (see for example, Rot, A., et al., J. Exp. Med., 1992, 176, 1489), chemotaxis of natural killer cells (see for example, Maghazachi, A.A., et al., J. Immunol., 1994, 153, 4969), expression of integrins (see for example, Vaddi, K., et al., J. Immunol., 1994, 153, 4721), and osteoclast differentiation (see for example, Kukita, T., et al., Lab. Invest., 1997, 76, 399). MIP-1α also enhances IgE and IgG4 production in B cells (see for example, Kimata, H., et al., J. Exp. Med., 1996, 183, 2397) and inhibits hematopoietic stem cell proliferation (see for example, Mayani, H., et al., Exp. Hematol., 1995, 23, 422; Keller, J.R., et al., Blood, 1994, 84, 2175; Eaves, C.J., et al., Proc. Natl. Acad. Sci. USA, 1993, 90, 12015; Bodine, D.M., et al., Blood, 1991, 78, 914; Broxmeyer, H.E., et al., Blood, 1990, 76, 1110).

With respect to the activity of MIP-1α in vivo and its role in the pathogenesis of disease, it has been reported that it is a pyrogen in rabbits (see for example Davatelis, G., et al., Science, 1989, 243, 1066); that MIP-1α injection into mouse foot pads results in an inflammatory reaction such as infiltration by neutrophils and mononuclear cells (see for example Alam, R., et al., J. Immunol., 1994, 152, 1298); that MIP-1α neutralizing antibody has an inhibitory effect or a therapeutic effect in animal models of granuloma (see for example Lukacs, N.W., et al., J. Exp. Med., 1993, 177, 1551), asthma (see for example Lukacs, N.W., et al., Eur. J. Immunol., 1995, 25, 245; Lukacs, N.W., et al., J. Immunol., 1997, 158, 4398), multiple sclerosis (see for example Karpus,

W.J., et al., J. Immunol., 1995, 155, 5003; Karpus, W.J., et al., J. Leukoc. Biol., 1997, 62, 681), idiopathic pulmonary fibrosis (see for example Smith, R.E., et al., J. Immunol., 1994, 153, 4704; Smith, R.E., Biol. Signals, 1996, 5, 223), acute lung injury (see for example Shanley, T.P., et al., J. Immunol., 1995, 154, 4793; Standiford, T.J., et al., J. Immunol., 1995, 155, 1515), and rheumatoid arthritis (see for example Kasama, T., et al., J. Clin. Invest., 1995, 95, 2868); that coxsackie virus induced myocarditis and herpes stromal keratitis are inhibited in mice with a disrupted MIP-1α gene (see for example Cook, D.N. et al., Science, 1995, 269, 1583; Tumpey, T.M., et al., J. Virology, 1998, 72, 3705); and that significant expression of MIP-1α is observed in patients with chronic inflammatory diseases of lung (see for example Standiford, T.J., et al., J. Immunol., 1993, 151, 2852), hypersensitivity pneumonitis (see for example Denis, M., Am. J. Respir. Crit. Care Med., 1995, 151, 164), rheumatoid arthritis (see for example Koch, A.E., et al., J. Clin. Invest., 1994, 93, 921), infectious meningitis (see for example Lahrtz, F., et al., J. Neuroimmunol., 1998, 85, 33), and chronic inflammation of muscle (see for example Adams, E.M., et al., Proc. Assoc. Am. Physicians, 1997, 109, 275). These studies indicate that MIP-1α is deeply involved in the local attraction of various subtypes of leukocytes and the initiation, progression and maintenance of resulting inflammatory response.

MCP-1 (also known as MCAF (abbreviation for macrophage chemotactic and activating factor) or JE) is a CC chemokine produced by monocytes/macrophages, smooth muscle cells, fibroblasts, and vascular endothelial cells and causes cell migration and cell adhesion of monocytes (see for example Valente, A.J., et al., Biochemistry, 1988, 27, 4162; Matsushima, K., et al., J. Exp. Med., 1989, 169, 1485; Yoshimura, T., et al., J. Immunol., 1989, 142, 1956; Rollins, B.J., et al., Proc. Natl. Acad. Sci. USA, 1988, 85, 3738; Rollins, B.J., et al., Blood, 1991, 78, 1112; Jiang, Y., et al., J. Immunol., 1992, 148, 2423; Vaddi, K., et al., J. Immunol., 1994, 153, 4721), memory T lymphocytes (see for example Carr, M.W., et al., Proc. Natl. Acad. Sci. USA, 1994, 91, 3652), T lymphocytes (see for example Loetscher, P., et al., FASEB J., 1994, 8, 1055) and natural killer cells (see for example Loetscher, P., et al., J. Immunol., 1996, 156, 322; Allavena, P., et al., Eur. J. Immunol., 1994, 24, 3233), as well as mediating histamine release by basophils (see for example Alam, R., et al., J. Clin. Invest., 1992, 89, 723; Bischoff, S.C., et al., J. Exp. Med., 1992, 175, 1271; Kuna, P., et al., J. Exp. Med., 1992, 175, 489).

In addition, high expression of MCP-1 has been reported in diseases where accumulation of monocyte/macrophage and/or T cells is thought to be important

in the initiation or progression of diseases, such as atherosclerosis (see for example Hayes, I.M., et al., Arterioscler. Thromb. Vasc. Biol., 1998, 18, 397; Takeya, M., et al., Hum. Pathol., 1993, 24, 534; Yla-Herttuala, S., et al., Proc. Natl. Acad. Sci. USA, 1991, 88, 5252; Nelken, N.A., J. Clin. Invest., 1991, 88, 1121), rheumatoid arthritis (see for example Koch, A.E., et al., J. Clin. Invest., 1992, 90, 772; Akahoshi, T., et al., Arthritis Rheum., 1993, 36, 762; Robinson, E., et al., Clin. Exp. Immunol., 101, 398), nephritis (see for example Noris, M., et al., Lab. Invest., 1995, 73, 804; Wada, T., at al., Kidney Int., 1996, 49, 761; Gesualdo, L., et al., Kidney Int., 1997, 51, 155), nephropathy (see for example Saitoh, A., et al., J. Clin. Lab. Anal., 1998, 12, 1; Yokoyama, H., et al., J. Leukoc. Biol., 1998, 63, 493), pulmonary fibrosis, pulmonary sarcoidosis (see for example Sugiyama, Y., et al., Internal Medicine, 1997, 36, 856), asthma (see for example Karina, M., et al., J. Invest. Allergol. Clin. Immunol., 1997, 7, 254; Stephene, T.H., Am. J. Respir. Crit. Care Med., 1997, 156, 1377; Sousa, A.R., et al., Am. J. Respir. Cell Mol. Biol., 1994, 10, 142), multiple sclerosis (see for example McManus, C., et al., J. Neuroimmunol., 1998, 86, 20), psoriasis (see for example Gillitzer, R., et al., J. Invest. Dermatol., 1993, 101, 127), inflammatory bowel disease (see for example Grimm, M.C., et al., J. Leukoc. Biol., 1996, 59, 804; Reinecker, H.C., et al., Gastroenterology, 1995, 106, 40), myocarditis (see for example Seino, Y., et al., Cytokine, 1995, 7, 301), endometriosis (see for example Jolicoeur, C., et al., Am. J. Pathol., 1998, 152, 125), intraperitoneal adhesion (see for example Zeyneloglu, H.B., et al., Human Reproduction, 1998, 13, 1194), congestive heart failure (see for example Aurust, P., et al., Circulation, 1998, 97, 1136), chronic liver disease (see for example Marra, F., et al., Am. J. Pathol., 1998, 152, 423), viral meningitis (see for example Lahrtz, F., et al., Eur. J. Immunol., 1997, 27, 2484), Kawasaki disease (see for example Wong, M.; et al., J. Rheumatol., 1997, 24,1179) and sepsis (see for example Salkowski, C.A.; et al., Infect. Immun., 1998, 66, 3569). Furthermore, anti-MCP-1 antibody has been reported to show an inhibitory effect or a therapeutic effect in animal models of rheumatoid arthritis (see for example Schimmer, R.C., et al., J. Immunol., 1998, 160, 1466; Schrier, D.J., J. Leukoc. Biol., 1998, 63, 359; Ogata, H., et al., J. Pathol., 1997, 182, 106), multiple sclerosis (see for example Karpus, W.J., et al., J. Leukoc. Biol., 1997, 62, 681), nephritis (see for example Lloyd, C.M., et al., J. Exp. Med., 1997, 185, 1371; Wada, T., et al., FASEB J., 1996, 10, 1418), Asthma (see for example Gonzalo, J.-A., et al., J. Exp. Med., 1998, 188, 157; Lukacs, N.W., J. Immunol., 1997, 158, 4398), atherosclerosis (see for example Guzman, L.A., et al.,

Circulation, 1993, 88 (suppl.), I-371), delayed type hypersensitivity (see for example Rand, M.L., et al., Am. J. Pathol., 1996, 148, 855), pulmonary hypertension (see for example Kimura, H., et al., Lab. Invest., 1998, 78, 571), and intraperitoneal adhesion (see for example Zeyneloglu, H.B., et al., Am. J. Obstet. Gynecol., 1998, 179, 438). A peptide antagonist of MCP-1, MCP-1(9-76), has been also reported to inhibit arthritis in the mouse model (see Gong, J.-H., J. Exp. Med., 1997, 186, 131), as well as studies in MCP-1-deficient mice have shown that MCP-1 is essential for monocyte recruitment in vivo (see Lu, B., et al., J. Exp. Med., 1998, 187, 601; Gu, L., et al., Moll. Cell, 1998, 2, 275).

These data indicate that chemokines such as MIP-1α and MCP-1 attract monocytes and lymphocytes to disease sites and mediate their activation and thus are thought to be intimately involved in the initiation, progression and maintenance of diseases deeply involving monocytes and lymphocytes, such as atherosclerosis, rheumatoid arthritis, psoriasis, asthma, ulcerative colitis, nephritis (nephropathy), multiple sclerosis, pulmonary fibrosis, myocarditis, hepatitis, pancreatitis, sarcoidosis, Crohn's disease, endometriosis, congestive heart failure, viral meningitis, cerebral infarction, neuropathy, Kawasaki disease, and sepsis (see for example Rovin, B.H., et al., Am. J. Kidney. Dis., 1998, 31, 1065; Lloyd, C., et al., Curr. Opin. Nephrol. Hypertens., 1998, 7, 281; Conti, P., et al., Allergy and Asthma Proc., 1998, 19, 121; Ransohoff, R.M., et al., Trends Neurosci., 1998, 21, 154; MacDermott, R.P., et al., Inflammatory Bowel Diseases, 1998, 4, 54). Therefore, drugs which inhibit the action of chemokines on target cells may be effective as a therapeutic and/or preventive drug in the diseases.

Genes encoding receptors of specific chemokines have been cloned, and it is now known that these receptors are G protein-coupled seven-transmembrane receptors present on various leukocyte populations. So far, at least five CXC chemokine receptors (CXCR1-CXCR5) and eight CC chemokine receptors (CCR1-CCR8) have been identified. For example IL-8 is a ligand for CXCR1 and CXCR2, MIP-1α is that for CCR1 and CCR5, and MCP-1 is that for CCR2A and CCR2B (for reference, see for example, Holmes, W.E., et al., Science 1991, 253, 1278-1280; Murphy P.M., et al., Science, 253, 1280-1283; Neote, K. et al., Cell, 1993, 72, 415-425; Charo, I.F., et al., Proc. Natl. Acad. Sci. USA, 1994, 91, 2752-2756; Yamagami, S., et al., Biochem. Biophys. Res. Commun., 1994, 202, 1156-1162; Combadier, C., et al., The Journal of Biological Chemistry, 1995, 270, 16491-16494, Power, C.A., et al., J. Biol. Chem., 1995, 270, 19495-19500; Samson, M., et al.,

Biochemistry, 1996, 35, 3362-3367; Murphy, P.M., Annual Review of Immunology, 1994, 12, 592-633). It has been reported that lung inflammation and granuroma formation are suppressed in CCR1-deficient mice (see Gao, J.-L., et al., J. Exp. Med., 1997, 185, 1959; Gerard, C., et al., J. Clin. Invest., 1997, 100, 2022), and that recruitment of macrophages and formation of atherosclerotic lesion decreased in CCR2-deficient mice (see Boring, L., et al., Nature, 1998, 394, 894; Kuziel, W.A., et al., Proc. Natl. Acad. Sci., USA, 1997, 94, 12053; Kurihara, T., et al., J. Exp. Med., 1997, 186, 1757; Boring, L., et al., J. Clin. Invest., 1997, 100, 2552). Therefore, compound which inhibit the binding of chemokines such as MIP-1α and/or MCP-1 to these receptors, that is, chemokine receptor antagonist, may be useful as drugs which inhibit the action of chemokines such as MIP-1α and/or MCP-1 on the target cells, but there are no drugs known to have such effects.

The cyclic amine derivatives provided by the present invention is quite novel. Recently, it has been reported that the diphenylmethane derivatives (WO9724325; Hesselgesser, J., et al., J. Biol. Chem., 1998, 273, 15687), piperidine derivatives (JP9-249566), imidazobenzodiazepine derivatives (JP9-249570), benzazocine derivatives (JP9-255572), tricyclic compounds with cyclic amino group (WO9804554), phenothiazine derivatives (Bright, C., et al., Bioorg. Med. Chem. Lett., 1998, 8, 771), pieprazine derivatives (WO9744329), benzimidazole derivatives (WO9806703), distamycin analogues (Howard, O.M.Z., et al., J. Med. Chem., 1998, 41, 2184), bis-acridine derivatives (WO9830218), spiro-substituted azacycles (WO9825604; WO9825605), substituted aryl piperazines (WO9825617), aminoquinoline derivatives (WO9827815), 3-arylpiperidine derivatives (WO9831364), hexanoic amide derivatives (WO9838167), and other small molecules (WO9744329; WO9802151; WO9804554) have antagonistic activity of chemokine receptor, such as CXCR1, CXCR4, CCR1, CCR2, CCR3, and CCR5. However, these compounds differ from the compound of the present invention.

Summary of the Invention

Therefore, it is an object of the present invention to provide small molecule compound which inhibits the binding of chemokines such as MIP-1α and/or MCP-1 to their receptors on the target cells.

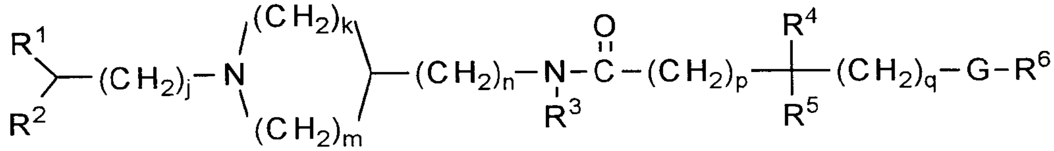
It is another object of the present invention to establish a method to inhibit the binding to the receptors on the target cells and/or effects on target cells of chemokines such as MIP-1α and/or MCP-1.

It is an additional object of the present invention to propose a method

for the treatment of diseases for which the binding of chemokines such as MIP-1α and/or MCP-1 to the receptor on the target cell is one of the causes.

As a result of intensive studies, the present inventors discovered that a cyclic amine derivative having a arylalkyl group, its pharmaceutically acceptable C_1–C_6 alkyl addition salt or its pharmaceutically acceptable acid addition salt has an excellent activity to inhibit the binding of chemokines such as MIP-1α and/or MCP-1 and the like to the receptor of a target cell, which has led to the completion of this invention.

That is, the present invention is a compound of the formula (I) below:



(I)

, a pharmaceutically acceptable acid addition salt thereof or a pharmaceutically acceptable C_1–C_6 alkyl addition salt thereof (**Invention 1**),

wherein R^1 is a phenyl group, a C_3–C_8 cycloalkyl group, or an aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof, in which the phenyl or aromatic heterocyclic group may be condensed with a benzene ring or an aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof, to form a condensed ring, and the phenyl group, C_3–C_8 cycloalkyl group, aromatic heterocyclic group, or condensed ring may be substituted with one or more of a halogen atom, a hydroxy group, a cyano group, a nitro group, a carboxy group, a carbamoyl group, a C_1–C_6 alkyl group, a C_3–C_8 cycloalkyl group, a C_2–C_6 alkenyl group, a C_1–C_6 alkoxy group, a C_1–C_6 alkylthio group, a C_3–C_5 alkylene group, a C_2–C_4 alkylenoxy group, a C_1–C_3 alkylenedioxy group, a phenyl group, a phenoxy group, a phenylthio group, a benzyl group, a benzyloxy group, a benzoylamino group, a C_2–C_7 alkanoyl group, a C_2–C_7 alkoxycarbonyl group, a C_2–C_7 alkanoyloxy group, a C_2–C_7 alkanoylamino group, a C_2–C_7 *N*-alkylcarbamoyl group, a C_4–C_9 *N*-cycloalkylcarbamoyl group, a C_1–C_6 alkylsulfonyl group, a C_3–C_8 (alkoxycarbonyl)methyl group, a *N*-phenylcarbamoyl group, a piperidinocarbonyl group, a morpholinocarbonyl group, a 1-pyrrolidinylcarbonyl group, a divalent group represented by the formula: -NH(C=O)O-, a divalent group represented by the formula: -NH(C=S)O-, an amino

group, a mono(C_1-C_6 alkyl)amino group, or a di(C_1-C_6 alkyl)amino group, wherein the substituent for the phenyl group, C_3-C_8 cycloalkyl group, aromatic heterocyclic group, or condensed ring is optionally substituted with one or more of a halogen atom, a hydroxy group, an amino group, a trifluoromethyl group, a C_1-C_6 alkyl group, or a C_1-C_6 alkoxy group;

R^2 is a hydrogen atom, a C_1-C_6 alkyl group, a C_2-C_7 alkoxycarbonyl group, a hydroxy group, or a phenyl group, in which the C_1-C_6 alkyl or phenyl group may be substituted with one or more of a halogen atom, a hydroxy group, a C_1-C_6 alkyl group, or a C_1-C_6 alkoxy group, and when j = 0, R^2 is not a hydroxy group;

j represents an integer of 0-2;

k represents an integer of 0-2;

m represents an integer of 2-4;

n represents 0 or 1;

R^3 is a hydrogen atom or a C_1-C_6 alkyl group optionally substituted with one or two phenyl groups each of which may be substituted with one or more of a halogen atom, a hydroxy group, a C_1-C_6 alkyl group, or a C_1-C_6 alkoxy group;

R^4 and R^5 are the same or different from each other and are a hydrogen atom, a hydroxy group, a phenyl group, or a C_1-C_6 alkyl group, in which the C_1-C_6 alkyl group is optionally substituted with one or more of a halogen atom, a hydroxy group, a cyano group, a nitro group, a carboxy group, a carbamoyl group, a mercapto group, a guanidino group, a C_3-C_8 cycloalkyl group, a C_1-C_6 alkoxy group, a C_1-C_6 alkylthio group, a phenyl group optionally substituted with one or more of a halogen atom, a hydroxy group, a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, or a benzyloxy group, a phenoxy group, a benzyloxy group, a benzyloxycarbonyl group, a C_2-C_7 alkanoyl group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 alkanoyloxy group, a C_2-C_7 alkanoylamino group, a C_2-C_7 *N*-alkylcarbamoyl group, a C_1-C_6 alkylsulfonyl group, an amino group, a mono(C_1-C_6 alkyl)amino group, a di(C_1-C_6 alkyl)amino group, or an aromatic heterocyclic group having 1-3 of heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof and optionally condensed with benzene ring, or R^4 and R^5 taken together form a 3 to 6 membered cyclic hydrocarbon;

p represents 0 or 1;

q represents 0 or 1;

G is a group represented by -CO-, -SO_2-, -CO-O-, -NR^7-CO-, -CO-NR^7-, -NH-CO-NH-, -NH-CS-NH-, -NR^7-SO_2-, -SO_2-NR^7-, -NH-CO-O-, or -O-CO-NH-, wherein R^7 is a hydrogen atom or a C_1-C_6 alkyl group, or R^7 taken together with R^5 represents C_2-C_5 alkylene group;

R^5 is a phenyl group, a C_3-C_8 cycloalkyl group, a C_3-C_8 cycloalkenyl group, a benzyl group, or an aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof, in which the phenyl, benzyl, or aromatic heterocyclic group may be condensed with a benzene ring or an aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof, to form a condensed ring, and the phenyl group, C_3-C_8 cycloalkyl group, C_3-C_8 cycloalkenyl group, benzyl group, aromatic heterocyclic group, or condensed ring may be substituted with one or more of a halogen atom, a hydroxy group, a mercapto group, a cyano group, a nitro group, a thiocyanato group, a carboxy group, a carbamoyl group, a trifluoromethyl group, a C_1-C_6 alkyl group, a C_3-C_6 cycloalkyl group, a C_2-C_6 alkenyl group, a C_1-C_6 alkoxy group, a C_3-C_8 cycloalkyloxy group, a C_1-C_6 alkylthio group, a C_1-C_3 alkylenedioxy group, a phenyl group, a phenoxy group, a phenylamino group, a benzyl group, a benzoyl group, a phenylsulfinyl group, a phenylsulfonyl group, a 3-phenylureido group, a C_2-C_7 alkanoyl group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 alkanoyloxy group, a C_2-C_7 alkanoylamino group, a C_2-C_7 *N*-alkylcarbamoyl group, a C_1-C_6 alkylsulfonyl group, a phenylcarbamoyl group, a *N,N*-di(C_1-C_6 alkyl)sulfamoyl group, an amino group, a mono(C_1-C_6 alkyl)amino group, a di(C_1-C_6 alkyl)amino group, a benzylamino group, a C_2-C_7 (alkoxycarbonyl)amino group, a C_1-C_6 (alkylsulfonyl)amino group, or a bis(C_1-C_6 alkylsulfonyl)amino group, wherein the substituent for the phenyl group, C_3-C_8 cycloalkyl group, C_3-C_8 cycloalkenyl group, benzyl group, aromatic heterocyclic group, or condensed ring is optionally substituted with one or more of a halogen atom, a cyano group, a hydroxy group, an amino group, trifluoromethyl group, a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a C_1-C_6 alkylthio group, a mono(C_1-C_6 alkyl)amino group, or a di(C_1-C_6 alkyl)amino group.

Also the present invention is a method of inhibiting the binding of a chemokine to the receptor of a target cell and/or its action on a target cell using a pharmaceutical preparation containing a therapeutically effective amount of a compound represented by the above formula (I), a pharmaceutically acceptable acid addition salt thereof, or a pharmaceutically acceptable C_1-C_6 alkyl addition salt thereof (**Invention 2**).

Here, the compound represented by the above formula (I) have activities to inhibit the binding of chemokines such as MIP-1α and/or MCP-1 and the like

to the receptor of a target cell and activities to inhibit physiological activities of cells caused by chemokines such as MIP-1α and/or MCP-1 and the like.

Description of the Preferred Embodiments

(1) On Invention 1

In the above formula (I), R^1 is a phenyl group, a C_3-C_8 cycloalkyl group, or an aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof, in which the phenyl or aromatic heterocyclic group may be condensed with a benzene ring or an aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof, to form a condensed ring, and the phenyl group, C_3-C_8 cycloalkyl group, aromatic heterocyclic group, or condensed ring may be substituted with one or more of a halogen atom, a hydroxy group, a cyano group, a nitro group, a carboxy group, a carbamoyl group, a C_1-C_6 alkyl group, a C_3-C_8 cycloalkyl group, a C_2-C_6 alkenyl group, a C_1-C_6 alkoxy group, a C_1-C_6 alkylthio group, a C_3-C_5 alkylene group, a C_2-C_4 alkylenoxy group, a C_1-C_3 alkylenedioxy group, a phenyl group, a phenoxy group, a phenylthio group, a benzyl group, a benzyloxy group, a benzoylamino group, a C_2-C_7 alkanoyl group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 alkanoyloxy group, a C_2-C_7 alkanoylamino group, a C_2-C_7 *N*-alkylcarbamoyl group, a C_4-C_9 *N*-cycloalkylcarbamoyl group, a C_1-C_6 alkylsulfonyl group, a C_3-C_8 (alkoxycarbonyl)methyl group, a *N*-phenylcarbamoyl group, a piperidinocarbonyl group, a morpholinocarbonyl group, a 1-pyrrolidinylcarbonyl group, a divalent group represented by the formula: -NH(C=O)O-, a divalent group represented by the formula: -NH(C=S)O-, an amino group, a mono(C_1-C_6 alkyl)amino group, or a di(C_1-C_6 alkyl)amino group.

The "C_3-C_8 cycloalkyl group" for R^1 means a cyclic alkyl group such as a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl group, specifically including a cyclopropyl, cyclopentyl, and cyclohexyl group.

The "aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof" for R^1 is specifically, for example, thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazinyl, triazolyl, oxadiazolyl (furazanyl),

thiadiazolyl group and the like, preferably including a thienyl, furyl, pyrrolyl, isoxazolyl, and pyridyl group.

The "condensed ring" for R^1 means a ring obtained by the condensation with a benzene ring or an aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom of a phenyl group or an aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom and/or a nitrogen atom, at any possible sites, suitably and specifically for example, naphthyl, indolyl, benzofuranyl, benzothienyl, quinolyl, benzimidazolyl, benzoxazolyl, benzotriazolyl, benzoxadiazolyl (benzofurazanyl), and benzothiadiazolyl group.

Among them, a phenyl group and an isoxazolyl group can be listed as a preferred specific example for R^1.

The "halogen atom" as a substituent for the phenyl group, C_3-C_8 cycloalkyl group, aromatic heterocyclic group, or condensed ring in R^1 includes a fluorine atom, chlorine atom, bromine atom, and iodine atom, suitably including a fluorine atom, chlorine atom, and bromine atom.

The "C_1-C_6 alkyl group" as a substituent for R^1 means a C_1-C_6 straight-chain or a branched alkyl group such as a methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, isopropyl, isobutyl, sec-butyl, *tert*-butyl, isopentyl, neopentyl, *tert*-pentyl, isohexyl, 2-methylpentyl, 1-ethylbutyl group, and the like, suitably specifically including a methyl, ethyl, propyl, and isopropyl group.

The "C_3-C_8 cycloalkyl group" as a substituent for R^1 is the same as defined for the aforementioned "C_3-C_8 cycloalkyl group" for R^1, where the same examples can be given for the preferred specific examples.

The "C_2-C_6 alkenyl group" as a substituent for R^1 means a C_2-C_6 straight-chain or a branched alkenyl group such as a vinyl, allyl, 1-propenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 4-pentenyl, 5-hexenyl, 4-methyl-3-pentenyl group, and the like, suitably specifically including a vinyl and 2-methyl-1-propenyl group.

The "C_1-C_6 alkoxy group" as a substituent for R^1 means group consisting of the aforementioned C_1-C_6 alkyl group and oxy group, specifically, for example, a methoxy and ethoxy group.

The "C_1-C_6 alkylthio group" as a substituent for R^1 means group consisting of the aforementioned C_1-C_6 alkyl group and thio group, specifically, for example,

a methylthio and ethylthio group.

The "C_3-C_5 alkylene group" as a substituent for R^1 means the C_3-C_5 divalent alkylene group such as a trimethylene, tetramethylene, pentamethylene, and 1-methyltrimethylene group, specifically, for example, a trimethylene and a tetramethylene group.

The "C_2-C_4 alkylenoxy group" as a substituent for R^1 means group consisting of the aforementioned C_2-C_4 divalent alkylene group and oxy group such as a ethylenoxy ($-CH_2CH_2O-$), trimethylenoxy ($-CH_2CH_2CH_2O-$), tetramethylenoxy ($-CH_2CH_2CH_2CH_2O-$), and 1,1-dimethylethylenoxy ($-CH_2C(CH_3)_2O-$) group, specifically, for example, a ethylenoxy and trimethylenoxy group.

The "C_1-C_3 alkylenedioxy group" as a substituent for R^1 means group consisting of C_1-C_3 divalent alkylene group and two oxy groups such as a methylenedioxy ($-OCH_2O-$), ethylenedioxy ($-OCH_2CH_2O-$), trimethylenedioxy ($-OCH_2CH_2CH_2O-$, and propylenedioxy ($-OCH_2CH(CH_3)O-$) group, specifically, for example, a methylenedioxy and ethylenedioxy group.

The "C_2-C_7 alkanoyl group" as a substituent for R^1 means C_2-C_7 straight-chain or branched alkanoyl group such as an acetyl, propanoyl, butanoyl, pentanoyl, hexanoyl, heptanoyl, isobutyryl, 3-methylbutanoyl, 2-methylbutanoyl, pivaloyl, 4-methylpentanoyl, 3,3-dimethylbutanoyl, 5-methylhexanoyl group, and the like, where the preferred and specific example includes an acetyl group.

The "C_2-C_7 alkoxycarbonyl group" as a substituent for R^1 means group consisting of the aforementioned C_1-C_6 alkoxy group and carbonyl group, preferably and specifically for example, a methoxycarbonyl and ethoxycarbonyl group.

The "C_2-C_7 alkanoyloxy group" as a substituent for R^1 means group consisting of the aforementioned C_2-C_7 alkanoyl group and oxy group, specifically, for example, an acetyloxy group.

The "C_2-C_7 alkanoylamino group" as a substituent for R^1 means group consisting of the aforementioned C_2-C_7 alkanoyl group and amino group, specifically, for example, an acetylamino group.

The "C_2-C_7 *N*-alkylcarbamoyl group" as a substituent for R^1 means group consisting of the aforementioned C_1-C_6 alkyl group and carbamoyl group, specifically, for example, a *N*-methylcarbamoyl and *N*-ethylcarbamoyl group.

The "C_4-C_9 *N*-cycloalkylcarbamoyl group" as a substituent for R^1 means group consisting of the aforementioned C_3-C_8 cycloalkyl group and carbamoyl group, specifically, for example, a *N*-cyclopentylcarbamoyl and *N*-cyclohexylcarbamoyl group.

The "C_1-C_6 alkylsulfonyl group" as a substituent for R^1 means group

consisting of the aforementioned C_1-C_6 alkyl group and sulfonyl group, preferably and specifically, for example, a methylsulfonyl group.

The "C_3-C_8 (alkoxycarbonyl)methyl group" as a substituent for R^1 means group consisting of the aforementioned C_2-C_7 alkoxycarbonyl group and methyl group, preferably and specifically for example, a (methoxycarbonyl)methyl and (ethoxycarbonyl)methyl group.

The "mono(C_1-C_6 alkyl)amino group" as a substituent for R^1 means amino group substituted with one of the aforementioned C_1-C_6 alkyl group, preferably and specifically, for example, a methylamino and ethyl amino group.

The "di(C_1-C_6 alkyl)amino group" as a substituent for R^1 means amino group substituted with the same or different two C_1-C_6 alkyl group aforementioned, preferably and specifically, for example, a dimethylamino, diethylamino, and *N*-ethyl-*N*-methylamino group.

Among them, a halogen atom, a hydroxy group, a C_1-C_6 alkyl group, a C_2-C_6 alkenyl group, a C_1-C_6 alkoxy group, a C_1-C_6 alkylthio group, a C_2-C_4 alkylenoxy group, a methylenedioxy group, a *N*-phenylcarbamoyl group, an amino group, a mono(C_1-C_6 alkyl)amino group, and a di(C_1-C_6 alkyl)amino group can be listed as a preferred specific example for substituent for the phenyl group, C_3-C_8 cycloalkyl group, aromatic heterocyclic group, or condensed ring in R^1.

Furthermore above substituent for the phenyl group, C_3-C_8 cycloalkyl group, aromatic heterocyclic group, or condensed ring in R^1 are optionally substituted with one or more of a halogen atom, a hydroxy group, an amino group, a trifluoromethyl group, a C_1-C_6 alkyl group, or a C_1-C_6 alkoxy group. The halogen atom, C_1-C_6 alkyl group, and C_1-C_6 alkoxy group are the same as defined for the aforementioned substituents for the phenyl group, C_3-C_8 cycloalkyl group, aromatic heterocyclic group, or condensed ring in R^1, and the same examples can be listed as preferred specific examples.

In the above formula (I), R^2 represents a hydrogen atom, a C_1-C_6 alkyl group, a C_2-C_7 alkoxycarbonyl group, a hydroxy group, or a phenyl group, in which the C_1-C_6 alkyl or phenyl group may be substituted with one or more of a halogen atom, a hydroxy group, a C_1-C_6 alkyl group, or a C_1-C_6 alkoxy group, and when $j = 0$, R^2 is not a hydroxy group.

The C_1-C_6 alkyl group and C_2-C_7 alkoxycarbonyl group for R^2 are the same as defined for the aforementioned substituent for the phenyl group, C_3-C_8

cycloalkyl group, aromatic heterocyclic group, or condensed ring in R^1, and the same examples can be listed as preferred specific examples.

The halogen atom, C_1-C_6 alkyl group, and C_1-C_6 alkoxy group as substituents for the C_1-C_6 alkyl or phenyl group in R^2 are the same as defined for the aforementioned substituent for the phenyl group, C_3-C_8 cycloalkyl group, aromatic heterocyclic group, or condensed ring in R^1, and the same examples can be listed as preferred specific examples.

Among them, a hydrogen atom is a preferred specific example for R^2.

In the above formula (I), j represents an integer of 0-2. It is particularly preferred for j to be 0.

In the above formula (I), k represents an integer of 0-2 and m represents an integer of 2-4. It is preferred to use a 2-substituted pyrrolidine in which k is 0 and m is 3, a 3-substituted pyrrolidine in which k is 1 and m is 2, a 3-substituted piperidine in which k is 1 and m is 3, a 4-substituted piperidine in which k is 2 and m is 2, or 3-substituted hexahydroazepine in which k is 1 and m is 4.

n in the above formula (I) represents 0 or 1.

Especially, 3-amidopyrrolidines in which k is 1, m is 2, and n is 0 and 4-(amidomethyl)piperidines in which k is 2 , m is 2, and n is 1 can be listed as a particularly preferred example.

R^3 in the above formula (I) represents a hydrogen atom or a C_1-C_6 alkyl group optionally substituted with one or two phenyl groups each of which may be substituted with one or more of a halogen atom, a hydroxy group, a C_1-C_6 alkyl group, or a C_1-C_6 alkoxy group.

The C_1-C_6 alkyl group for R^3 is the same as defined for the aforementioned substituents for the phenyl group, C_3-C_8 cycloalkyl group, aromatic heterocyclic group, or condensed ring in R^1, specifically, for example, a methyl, ethyl and propyl group.

The halogen atom, C_1-C_6 alkyl group, and C_1-C_6 alkoxy group as substituents for the phenyl group, which is a substituent for C_1-C_6 alkyl group in R^3, are the same as defined for the aforementioned substituents for the phenyl group, C_3-C_8 cycloalkyl group, aromatic heterocyclic group, or condensed ring in R^1, and the same examples can be listed as preferred specific examples.

Among them, a hydrogen atom is a preferred specific example for R^3.

In the above formula (I), R^4 and R^5 are the same or different from each other and are a hydrogen atom, a hydroxy group, a phenyl group, or a C_1-C_6 alkyl group, in which the C_1-C_6 alkyl group is optionally substituted with one or more of a halogen atom, a hydroxy group, a cyano group, a nitro group, a carboxy group, a carbamoyl group, a mercapto group, a guanidino group, a C_3-C_8 cycloalkyl group, a C_1-C_6 alkoxy group, a C_1-C_6 alkylthio group, a phenyl group optionally substituted with one or more of a halogen atom, a hydroxy group, a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, or a benzyloxy group, a phenoxy group, a benzyloxy group, a benzyloxycarbonyl group, a C_2-C_7 alkanoyl group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 alkanoyloxy group, a C_2-C_7 alkanoylamino group, a C_2-C_7 *N*-alkylcarbamoyl group, a C_1-C_6 alkylsulfonyl group, an amino group, a mono(C_1-C_6 alkyl)amino group, a di(C_1-C_6 alkyl)amino group, or an aromatic heterocyclic group having 1-3 of heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof and optionally condensed with benzene ring, or R^4 and R^5 taken together form a 3 to 6 membered cyclic hydrocarbon.

The C_1-C_6 alkyl group for R^4 and R^5 is the same as defined for the aforementioned substituent for the phenyl group, C_3-C_8 cycloalkyl group, aromatic heterocyclic group, or condensed ring in R^1, and the same examples can be listed as preferred specific examples.

The halogen atom, C_1-C_6 alkoxy group, C_1-C_6 alkylthio group, C_2-C_7 alkanoyl group, C_2-C_7 alkoxycarbonyl group, C_2-C_7 alkanoyloxy group, C_2-C_7 alkanoylamino group, C_2-C_7 *N*-alkylcarbamoyl group, C_1-C_6 alkylsulfonyl group, mono(C_1-C_6 alkyl)amino group, and di(C_1-C_6 alkyl)amino group as a substituent for the C_1-C_6 alkyl group in R^4 and R^5 are the same as defined for the aforementioned substituent for the phenyl group, C_3-C_8 cycloalkyl group, aromatic heterocyclic group, or condensed ring in R^1, and the same examples can be listed as preferred specific examples.

The C_3-C_8 cycloalkyl group and aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof as substituent for the C_1-C_6 alkyl group in R^4 and R^5 are the same as defined for the aforementioned group for R^1, and the same examples can be listed as preferred specific examples.

The halogen atom, C_1-C_6 alkyl group, and C_1-C_6 alkoxy group for the substituent for the phenyl group which is substituent for the C_1-C_6 alkyl group in R^4 and R^5 are the same as defined for the aforementioned substituent for the phenyl group, C_3-C_8 cycloalkyl group, aromatic heterocyclic group, or condensed

ring in R^1, and the same examples can be listed as preferred specific examples.

The "3 to 6 membered cyclic hydrocarbon" consisting of R^4, R^5, and the adjacent carbon atom includes a cyclopropane, cyclobutane, cyclopentane, and cyclohexane.

Among them, a hydrogen atom and a C_1-C_6 alkyl group can be listed as a preferred specific example for R^4 and R^5.

In the above formula (I), p represents 0 or 1, and q represents 0 or 1. It is particularly preferred for both p and q to be 0.

In the above formula (I), G is a group represented by -CO-, $-SO_2-$, -CO-O-, $-NR^7-CO-$, $-CO-NR^7-$, -NH-CO-NH-, -NH-CS-NH-, $-NR^7-SO_2-$, $-SO_2-NR^7-$, -NH-CO-O-, or -O-CO-NH-, wherein R^7 is a hydrogen atom or a C_1-C_6 alkyl group, or R^7 taken together with R^5 represents a C_2-C_5 alkylene group.

In the above formula, -CO- means a carbonyl group, $-SO_2-$ means a sulfonyl group, and -CS- means a thiocarbonyl group. Preferred G group is specifically, for example, those represented by the formula $-NR^7-CO-$ and -NH-CO-NH-.

The C_1-C_6 alkyl group for R^7 are the same as defined for the aforementioned substituent for the phenyl group, C_3-C_8 cycloalkyl group, aromatic heterocyclic group, or condensed ring in R^1, and the same examples can be listed as preferred specific examples.

The "C_2-C_5 alkylene group" consisting of R^5 and R^7 means C_2-C_5 straight-chain or branched alkylene group such as a methylene, ethylene, propylene, trimethylene, tetramethylene, 1-methyltrimethylene, pentamethylene group, and the like, suitably and specifically including a ethylene, trimethylene and tetramethylene group.

A hydrogen atom is a preferred specific example for R^7.

In the above formula (I), R^6 is a phenyl group, a C_3-C_8 cycloalkyl group, a C_3-C_8 cycloalkenyl group, a benzyl group, or an aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof, in which the phenyl, benzyl, or aromatic heterocyclic group may be condensed with a benzene ring or an aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof, to form a condensed ring, and the phenyl group, C_3-C_8 cycloalkyl group, C_3-C_8 cycloalkenyl group, benzyl group, aromatic heterocyclic group, or condensed

ring may be substituted with one or more of a halogen atom, a hydroxy group, a mercapto group, a cyano group, a nitro group, a thiocyanato group, a carboxy group, a carbamoyl group, a trifluoromethyl group, a C_1-C_6 alkyl group, a C_3-C_6 cycloalkyl group, a C_2-C_6 alkenyl group, a C_1-C_6 alkoxy group, a C_3-C_8 cycloalkyloxy group, a C_1-C_6 alkylthio group, a C_1-C_3 alkylenedioxy group, a phenyl group, a phenoxy group, a phenylamino group, a benzyl group, a benzoyl group, a phenylsulfinyl group, a phenylsulfonyl group, a 3-phenylureido group, a C_2-C_7 alkanoyl group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 alkanoyloxy group, a C_2-C_7 alkanoylamino group, a C_2-C_7 *N*-alkylcarbamoyl group, a C_1-C_6 alkylsulfonyl group, a phenylcarbamoyl group, a *N,N*-di(C_1-C_6 alkyl)sulfamoyl group, an amino group, a mono(C_1-C_6 alkyl)amino group, a di(C_1-C_6 alkyl)amino group, a benzylamino group, a C_2-C_7 (alkoxycarbonyl)amino group, a C_1-C_6 (alkylsulfonyl)amino group, or a bis(C_1-C_6 alkylsulfonyl)amino group.

The C_3-C_8 cycloalkyl group, aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof, and the condensed ring for R^6 are the same as defined for the aforementioned R^1, and the same examples can be listed as preferred specific examples.

The "C_3-C_8 cycloalkenyl group" for R^6 means a cyclic alkenyl group such as a cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl group, specifically including a 1-cyclopentenyl and 1-cyclohexenyl group.

Among them, a phenyl group, a furyl group, and a thienyl group can be listed as a preferred specific example for R^6.

The halogen atom, C_1-C_6 alkyl group, C_2-C_6 alkenyl group, C_1-C_6 alkoxy group, C_1-C_6 alkylthio group, C_1-C_3 alkylenedioxy group, C_2-C_7 alkanoyl group, C_2-C_7 alkoxycarbonyl group, C_2-C_7 alkanoyloxy group, C_2-C_7 alkanoylamino group, C_2-C_7 *N*-alkylcarbamoyl group, C_1-C_6 alkylsulfonyl group, mono(C_1-C_6 alkyl)amino group, and di(C_1-C_6 alkyl)amino group as a substituent for the phenyl group, C_3-C_8 cycloalkyl group, C_3-C_8 cycloalkenyl group, benzyl group, aromatic heterocyclic group, or condensed ring in R^6 are the same as defined for the aforementioned substituent for the phenyl group, C_3-C_8 cycloalkyl group, aromatic heterocyclic group, or condensed ring in R^1, and the same examples can be listed as preferred specific examples.

The C_3-C_8 cycloalkyl group as a substituent for R^6 is the same as defined for the aforementioned C_3-C_8 cycloalkyl group for R^1, where the same examples

can be given for the preferred specific examples.

The "C_3-C_8 cycloalkyloxy group" as a substituent for R^6 means group consisting of the aforementioned C_3-C_8 cycloalkyl group and oxy group, specifically, for example, a cyclopropyloxy, cyclopentyloxy, and cyclohexyloxy group.

The "*N*,*N*-di(C_1-C_6 alkyl)sulfamoyl group" as a substituent for R^6 means sulfamoyl group substituted with the same or different two C_1-C_6 alkyl group aforementioned, preferably and specifically, for example, a *N*,*N*-dimethylsulfamoyl, *N*,*N*-diethylsulfamoyl, and *N*-ethyl-*N*-methylsulfamoyl group.

The "C_2-C_7 (alkoxycarbonyl)amino group" as a substituent for R^6 means group consisting of the aforementioned C_2-C_7 alkoxycarbonyl group and amino group, specifically, for example, a (methoxycarbonyl)amino and (ethoxycarbonyl)amino group.

The "C_1-C_6 (alkylsulfonyl)amino" group as a substituent for R^6 means group consisting of the aforementioned C_1-C_6 alkylsulfonyl group and amino group, specifically, for example, a (methylsulfonyl)amino group.

The "bis(C_1-C_6 alkylsulfonyl)amino" group as a substituent for R^6 means amino group substituted with the same or different two C_1-C_6 alkylsulfonyl group aforementioned, preferably and specifically, for example, a bis(methylsulfonyl)amino group.

Among them, a halogen atom, a mercapto group, a nitro group, a thiocyanato group, a trifluoromethyl group, a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a phenyl group, a phenylsulfonyl group, a C_2-C_7 alkanoylamino group, or an amino group can be listed as preferred specific example for substituent for the phenyl group, C_3-C_8 cycloalkyl group, C_3-C_8 cycloalkenyl group, benzyl group, aromatic heterocyclic group, or condensed ring in R^6.

Furthermore above substituents for the phenyl group, C_3-C_8 cycloalkyl group, C_3-C_8 cycloalkenyl group, benzyl group, aromatic heterocyclic group, or condensed ring in R^6 are optionally substituted with one or more of a halogen atom, a cyano group, a hydroxy group, an amino group, trifluoromethyl group, a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a C_1-C_6 alkylthio group, a mono(C_1-C_6 alkyl)amino group, or a di(C_1-C_6 alkyl)amino group.

The halogen atom, C_1-C_6 alkyl group, C_1-C_6 alkoxy group, a C_1-C_6 alkylthio group, mono(C_1-C_6 alkyl)amino group, and di(C_1-C_6 alkyl)amino group are the same as defined for the aforementioned substituents for the phenyl group, C_3-C_8 cycloalkyl group, aromatic heterocyclic group, or condensed ring in R^1, and the

same examples can be listed as preferred specific examples.

(2) On Invention 2

The compound represented by the formula (I) above, a pharmaceutically acceptable acid addition salt thereof or a pharmaceutically acceptable C_1-C_6 alkyl addition salt can be used to prepare a chemokine receptor antagonist preparation of the present invention by formulating the therapeutically effected amount and a carrier and/or diluent into a pharmaceutical composition. Thus, the cyclic amine derivatives shown by the above formula (I) , a pharmaceutically acceptable acid addition salt thereof or a pharmaceutically acceptable C_1-C_6 alkyl addition salt can be administered orally or by parenterally, for example, intravenously, subcutaneously, intramuscularly, percutaneously or intrarectally.

The oral administration can be accomplished in the form of tablets, pills, granules, powder, solution, suspension, capsules, etc.

The tablets for example can be prepared using a vehicle such as lactose, starch and crystallized cellulose; binder such as carboxymethylcellulose, methylcellulose, and polyvinylpyrrolidone; disintegrator such as sodium alginate, sodium bicarbonate and sodium lauryl sulfate, etc.

Pills, powder and granule preparations can be prepared by a standard method using the vehicles mentioned above. Solution or suspension can be prepared by a standard method using glycerin ester such as tricaprylin and triacetin or alcohols such as ethanol. Capsules can be made by charging granules, powder or solution in gelatin, etc.

Subcutaneous, intramuscular or intravenous preparations can be prepared as an injection using aqueous or nonaqueous solution. Aqueous solution for example may include isotonic sodium chloride solution. Nonaqueous solutions may include for example, propyleneglycol, polyethyleneglycol, olive oil, ethyl oleate, etc., and optionally, one can add antiseptics and stabilizers. For injection, one can be sterilized by filtration through a bacterial filter or combination of disinfectant.

Percutaneous administration may be in the form of an ointment or cream, and ointment can be prepared in the standard manner using fatty oils such as

castor oil and olive oil, or Vaseline, while creams can be made using fatty oils or emulsifying agent such as diethyleneglycol and sorbitan esters of fatty acid.

For intrarectal administration, one can use standard suppositories using gelatin soft capsules, etc.

The cyclic amine derivatives of the present invention, a pharmaceutically acceptable acid addition salt thereof or a pharmaceutically acceptable C_1-C_6 alkyl addition salt is administered at a dose that varies depending on the type of disease, route of administration, age and sex of patient, and severity of disease, but is likely to be 1-500 mg/day in an average adult.

(3) Matter common throughout Invention 1 and Invention 2

Preferred specific examples for the cyclic amine compound in the above formula (I) include compound having each substituent as shown in the following Tables 1.1—1.201.

In the Tables 1.1—1.201, "chirality" means configuration of the asymmetric carbon atom on the cyclic amine. "R" shows that the asymmetric carbon atom has a *R* configuration, "S" shows that the asymmetric carbon atom has a *S* configuration, and "-" means racemate or that the compound do not have a asymmetric carbon atom on the nitrogen containing ring.

[Table 1.1 - Table 1.201]

Table 1.1

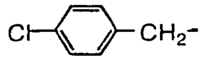
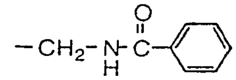
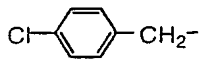
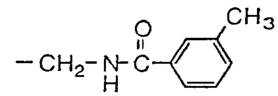
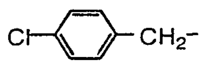
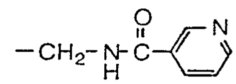
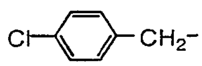
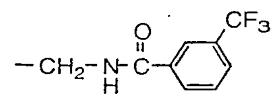
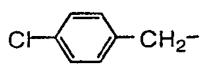
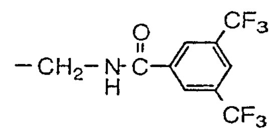
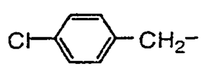
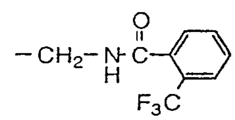
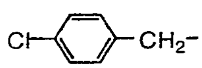
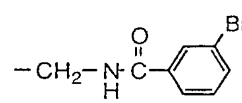
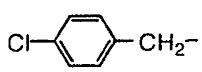
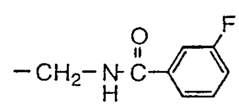
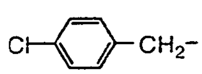
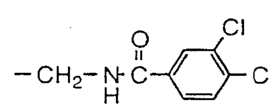
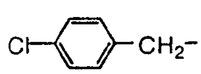
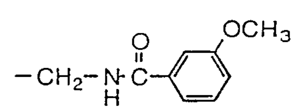
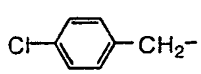
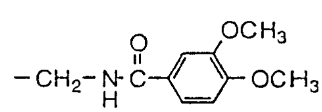
Compd. No.	$R^1R^2>-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1		1	2	0	-	H	
2		1	2	0	-	H	
3		1	2	0	-	H	
4		1	2	0	-	H	
5		1	2	0	S	H	
6		1	2	0	S	H	
7		1	2	0	S	H	
8		1	2	0	S	H	
9		1	2	0	S	H	
10		1	2	0	S	H	
11		1	2	0	S	H	

Table 1.2

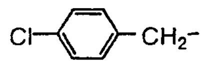
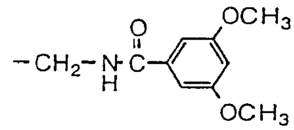
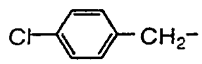
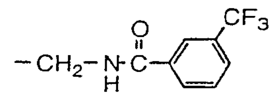
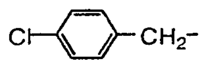
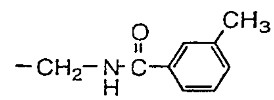
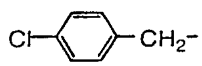
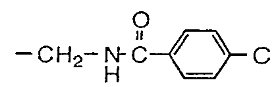
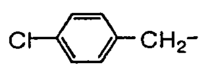
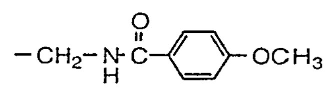
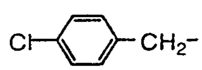
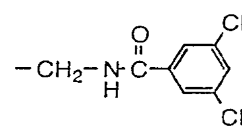
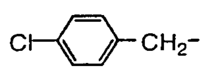
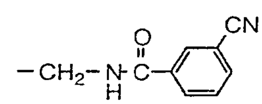
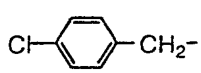
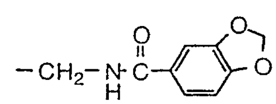
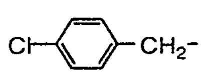
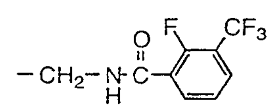
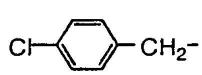
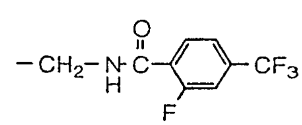
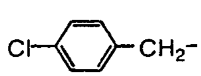
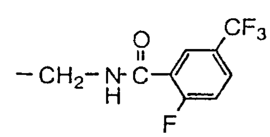
Compd. No.	$R^1(R^2)>(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
12		1	2	0	S	H	
13		1	2	0	S	H	
14		1	2	0	S	H	
15		1	2	0	S	H	
16		1	2	0	S	H	
17		1	2	0	S	H	
18		1	2	0	S	H	
19		1	2	0	S	H	
20		1	2	0	S	H	
21		1	2	0	S	H	
22		1	2	0	S	H	

Table 1.3

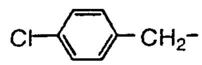
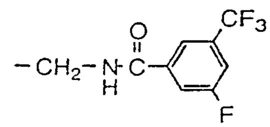
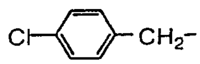
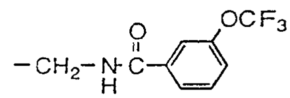
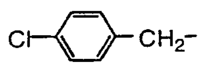
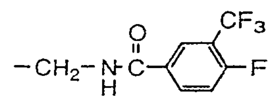
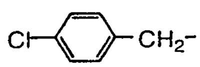
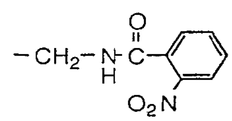
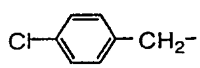
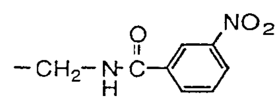
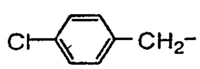
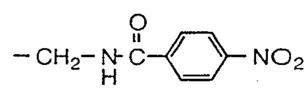
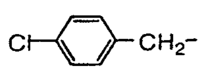
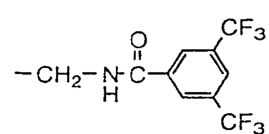
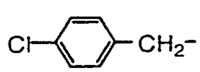
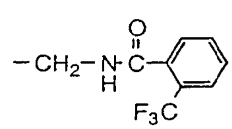
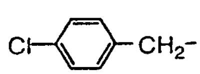
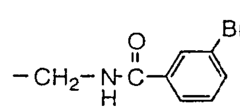
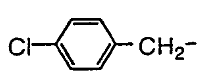
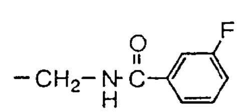
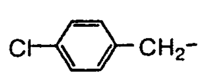
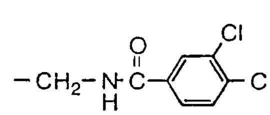
Compd. No.	$R^1R^2>(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
23		1	2	0	S	H	
24		1	2	0	S	H	
25		1	2	0	S	H	
26		1	2	0	S	H	
27		1	2	0	S	H	
28		1	2	0	S	H	
29		1	2	0	R	H	
30		1	2	0	R	H	
31		1	2	0	R	H	
32		1	2	0	R	H	
33		1	2	0	R	H	

Table 1.4

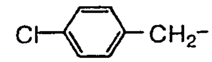
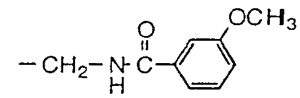
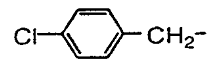
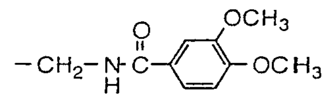
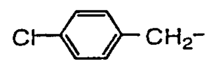
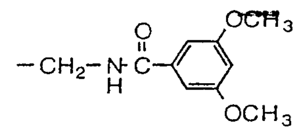
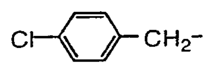
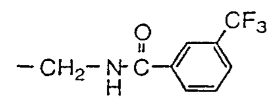
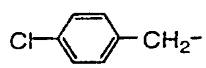
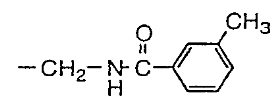
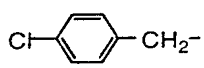
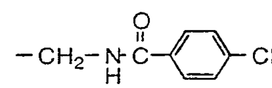
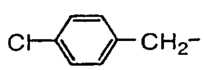
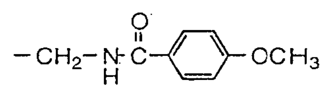
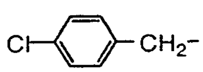
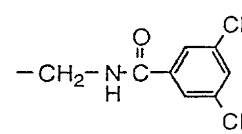
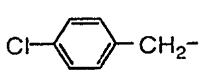
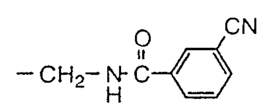
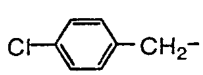
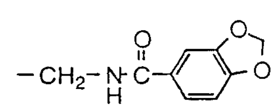
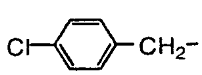
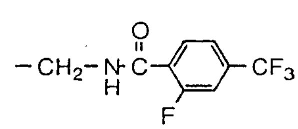
Compd. No.	$R^1R^2>-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
34		1	2	0	R	H	
35		1	2	0	R	H	
36		1	2	0	R	H	
37		1	2	0	R	H	
38		1	2	0	R	H	
39		1	2	0	R	H	
40		1	2	0	R	H	
41		1	2	0	R	H	
42		1	2	0	R	H	
43		1	2	0	R	H	
44		1	2	0	R	H	

Table 1.5

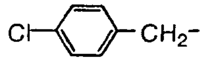
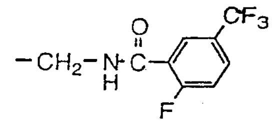
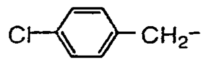
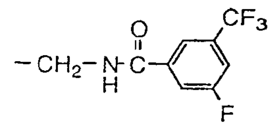
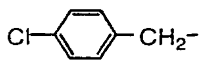
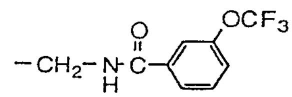
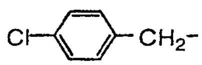
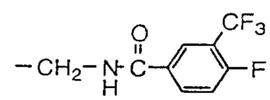
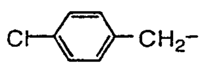
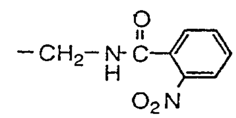
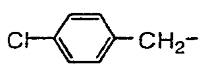
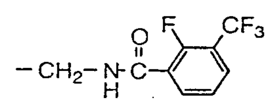
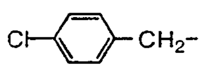
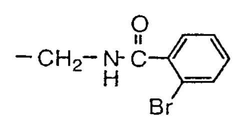
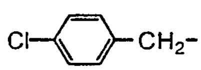
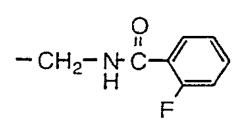
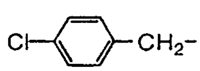
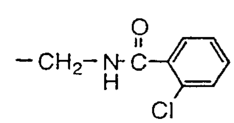
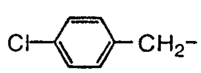
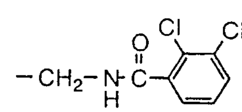
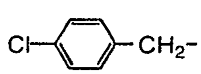
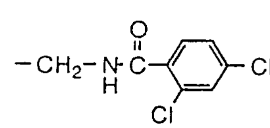
Compd. No.	$R^1R^2>-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
45		1	2	0	R	H	
46		1	2	0	R	H	
47		1	2	0	R	H	
48		1	2	0	R	H	
49		1	2	0	R	H	
50		1	2	0	R	H	
51		1	2	0	R	H	
52		1	2	0	R	H	
53		1	2	0	R	H	
54		1	2	0	R	H	
55		1	2	0	R	H	

Table 1.6

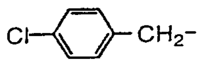
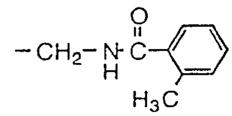
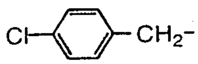
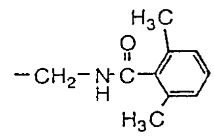
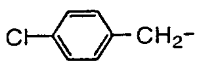
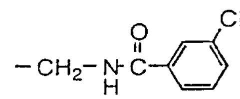
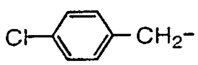
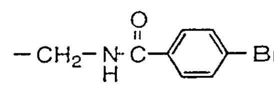
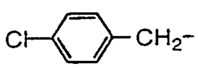
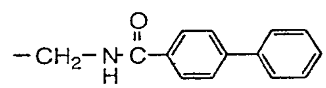
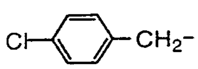
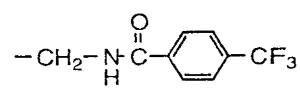
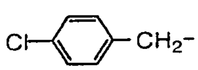
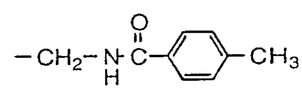
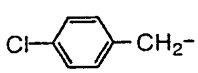
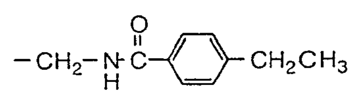
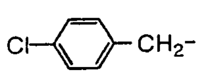
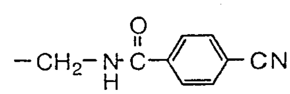
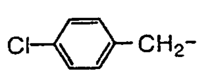
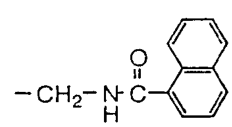
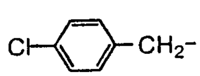
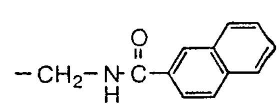
Compd. No.	$R^1R^2>-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
56		1	2	0	R	H	
57		1	2	0	R	H	
58		1	2	0	R	H	
59		1	2	0	R	H	
60		1	2	0	R	H	
61		1	2	0	R	H	
62		1	2	0	R	H	
63		1	2	0	R	H	
64		1	2	0	R	H	
65		1	2	0	R	H	
66		1	2	0	R	H	

Table 1.7

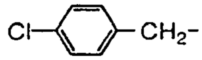
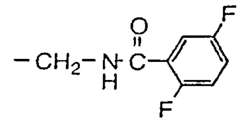
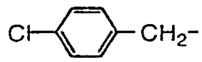
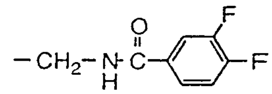
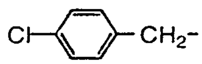
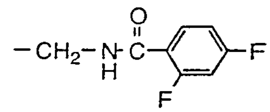
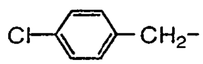
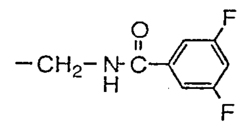
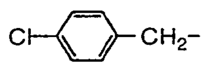
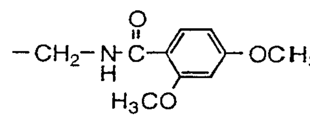
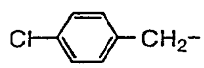
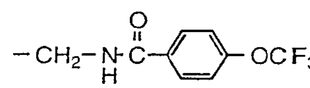
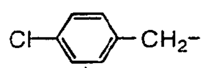
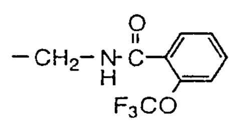
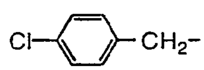
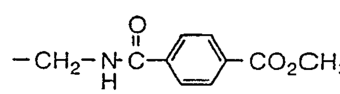
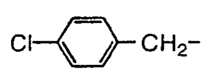
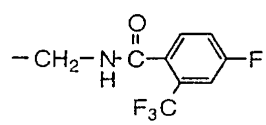
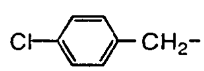
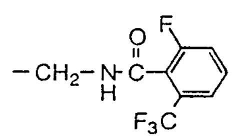
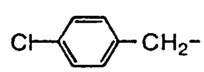
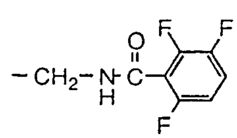
Compd. No.	$R^1R^2>(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
67		1	2	0	R	H	
68		1	2	0	R	H	
69		1	2	0	R	H	
70		1	2	0	R	H	
71		1	2	0	R	H	
72		1	2	0	R	H	
73		1	2	0	R	H	
74		1	2	0	R	H	
75		1	2	0	R	H	
76		1	2	0	R	H	
77		1	2	0	R	H	

Table 1.8

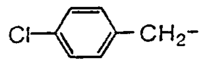
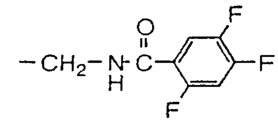
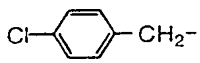
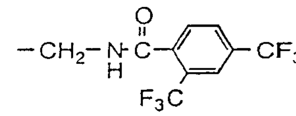
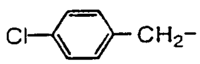
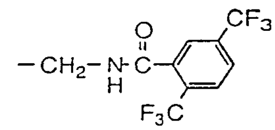
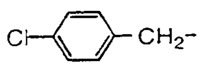
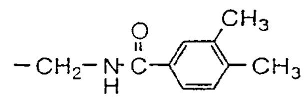
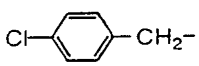
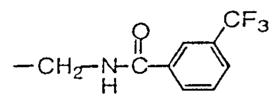
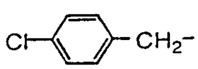
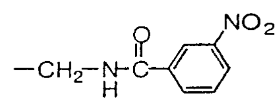
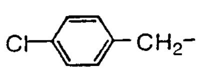
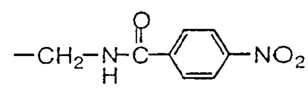
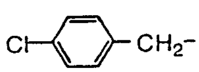
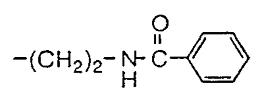
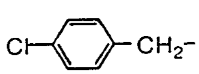
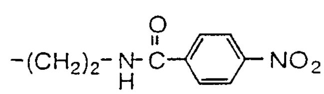
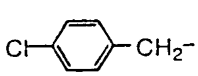
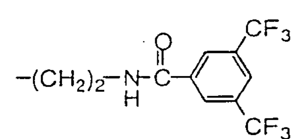
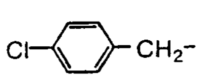
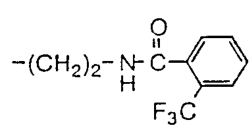
Compd. No.	$R^1R^2>$-$(CH_2)_j$-	k	m	n	chirality	R^3	-$(CH_2)_p$-$C(R^4)(R^5)$-$(CH_2)_q$-G-R^6
78		1	2	0	R	H	
79		1	2	0	R	H	
80		1	2	0	R	H	
81		1	2	0	R	H	
82		1	2	0	-	$-CH_3$	
83		1	2	0	R	H	
84		1	2	0	R	H	
85		1	2	0	-	H	
86		1	2	0	-	H	
87		1	2	0	S	H	
88		1	2	0	S	H	

Table 1.9

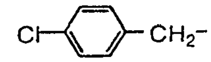
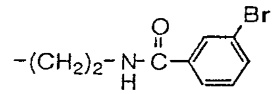
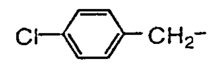
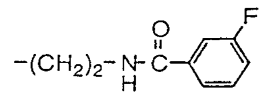
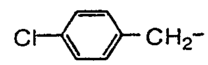
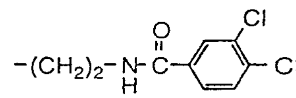
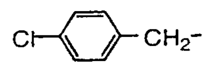
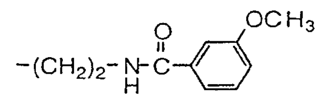
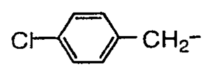
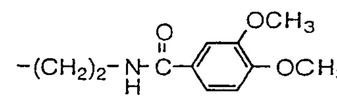
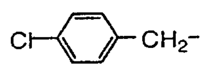
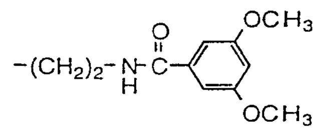
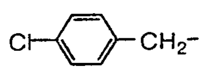
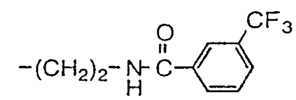
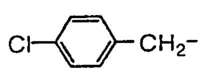
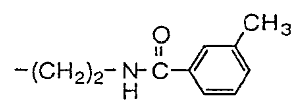
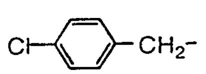
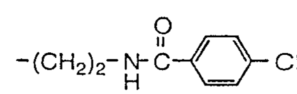
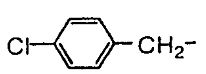
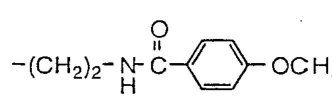
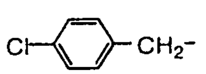
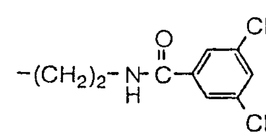
Compd. No.	$\begin{matrix}R^1\\R^2\end{matrix}\rangle-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
89		1	2	0	S	H	
90		1	2	0	S	H	
91		1	2	0	S	H	
92		1	2	0	S	H	
93		1	2	0	S	H	
94		1	2	0	S	H	
95		1	2	0	S	H	
96		1	2	0	S	H	
97		1	2	0	S	H	
98		1	2	0	S	H	
99		1	2	0	S	H	

Table 1.10

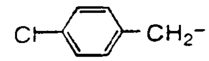
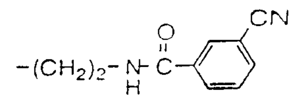
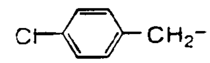
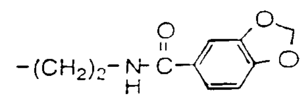
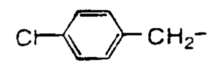
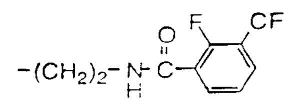
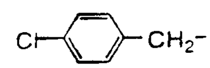
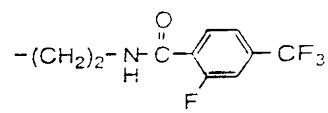
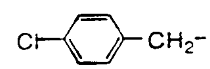
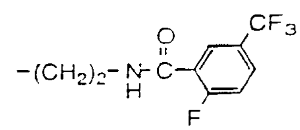
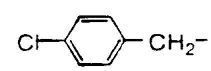
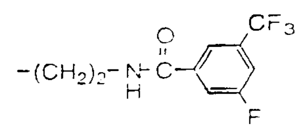
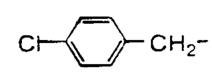
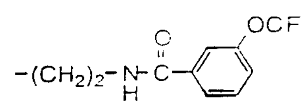
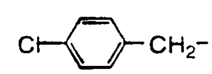
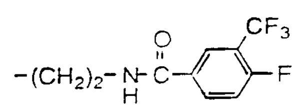
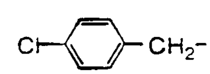
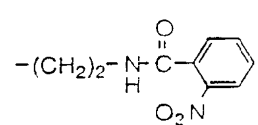
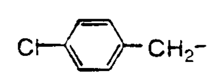
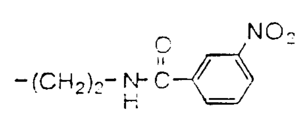
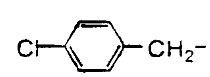
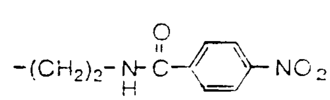
Compd. No.	$R^1R^2>-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
100		1	2	0	S	H	
101		1	2	0	S	H	
102		1	2	0	S	H	
103		1	2	0	S	H	
104		1	2	0	S	H	
105		1	2	0	S	H	
106		1	2	0	S	H	
107		1	2	0	S	H	
108		1	2	0	S	H	
109		1	2	0	S	H	
110		1	2	0	S	H	

Table 1.11

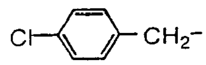
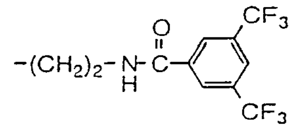
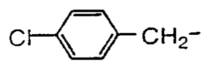
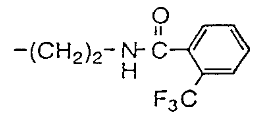
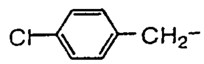
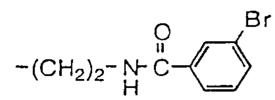
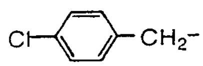
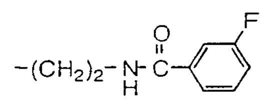
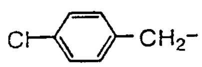
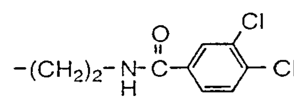
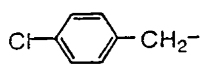
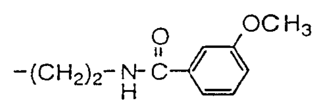
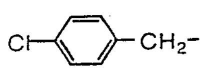
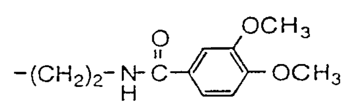
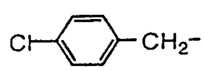
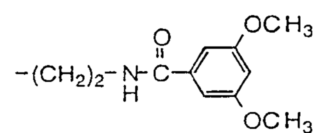
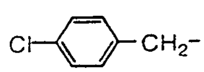
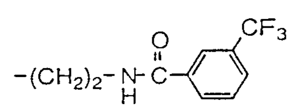
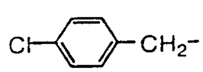
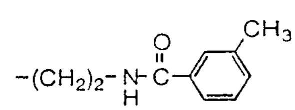
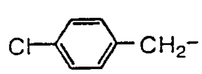
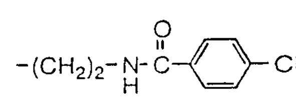
Compd. No.	R^1, R^2 >$-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
111		1	2	0	R	H	
112		1	2	0	R	H	
113		1	2	0	R	H	
114		1	2	0	R	H	
115		1	2	0	R	H	
116		1	2	0	R	H	
117		1	2	0	R	H	
118		1	2	0	R	H	
119		1	2	0	R	H	
120		1	2	0	R	H	
121		1	2	0	R	H	

Table 1.12

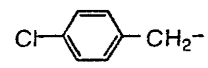
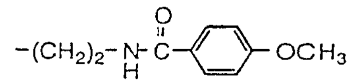
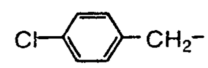
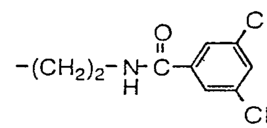
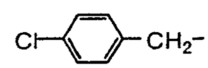
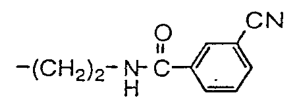
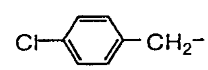
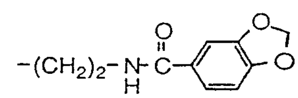
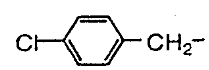
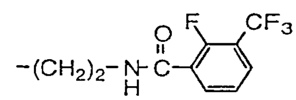
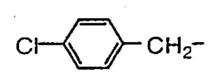
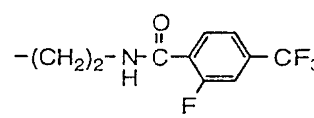
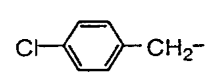
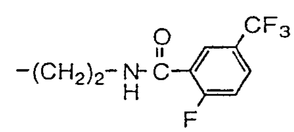
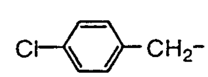
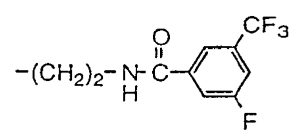
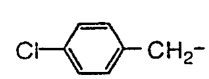
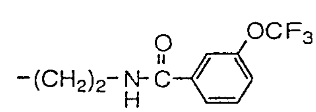
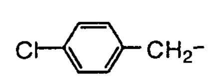
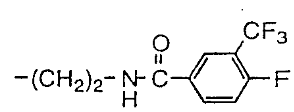
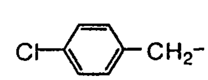
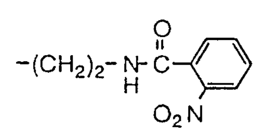
Compd. No.	$R^1R^2>-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
122		1	2	0	R	H	
123		1	2	0	R	H	
124		1	2	0	R	H	
125		1	2	0	R	H	
126		1	2	0	R	H	
127		1	2	0	R	H	
128		1	2	0	R	H	
129		1	2	0	R	H	
130		1	2	0	R	H	
131		1	2	0	R	H	
132		1	2	0	R	H	

Table 1.13

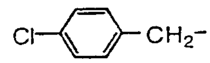
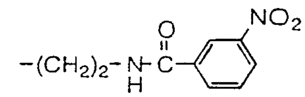
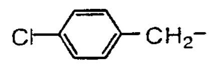
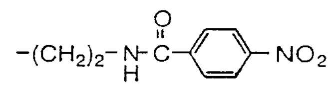
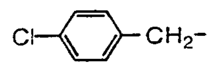
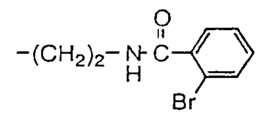
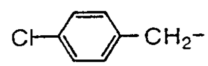
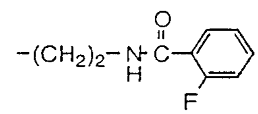
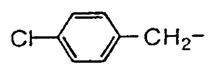
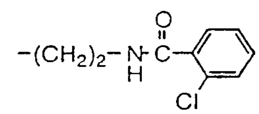
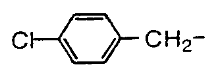
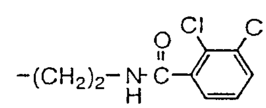
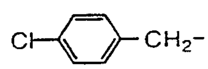
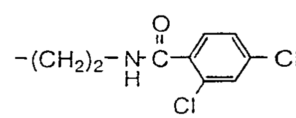
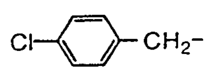
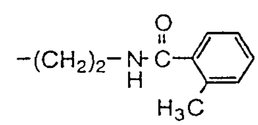
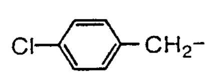
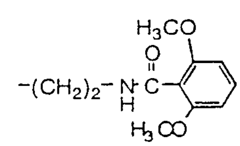
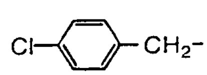
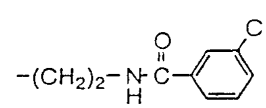
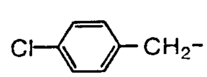
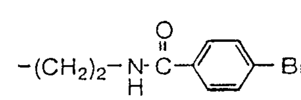
Compd. No.	$R^1R^2>$-$(CH_2)_j$-	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
133		1	2	0	R	H	
134		1	2	0	R	H	
135		1	2	0	R	H	
136		1	2	0	R	H	
137		1	2	0	R	H	
138		1	2	0	R	H	
139		1	2	0	R	H	
140		1	2	0	R	H	
141		1	2	0	R	H	
142		1	2	0	R	H	
143		1	2	0	R	H	

Table 1.14

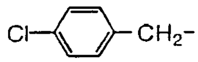
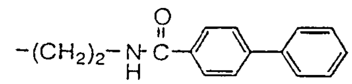
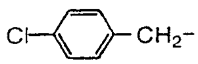
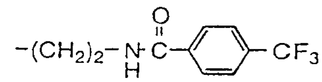
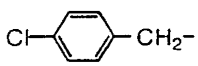
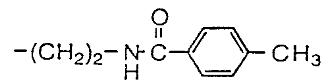
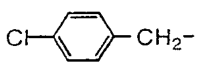
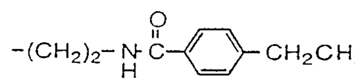
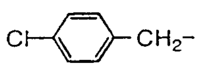
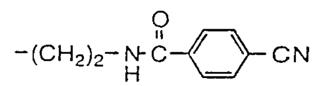
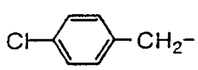
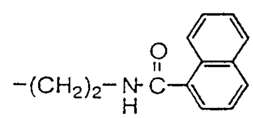
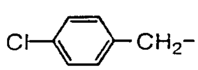
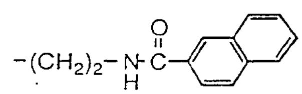
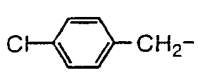
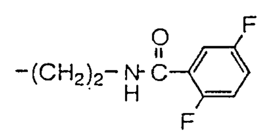
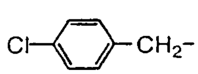
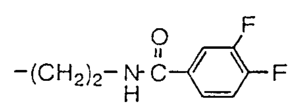
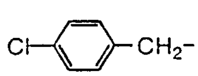
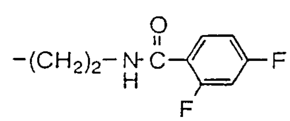
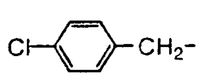
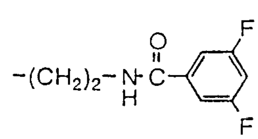
Compd. No.	$R^1R^2{>}(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
144		1	2	0	R	H	
145		1	2	0	R	H	
146		1	2	0	R	H	
147		1	2	0	R	H	
148		1	2	0	R	H	
149		1	2	0	R	H	
150		1	2	0	R	H	
151		1	2	0	R	H	
152		1	2	0	R	H	
153		1	2	0	R	H	
154		1	2	0	R	H	

Table 1.15

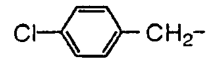
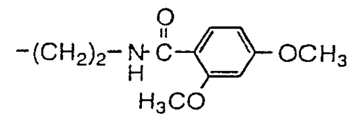
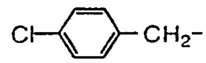
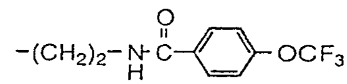
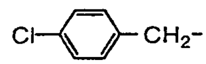
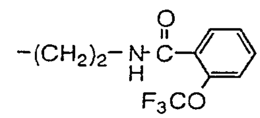
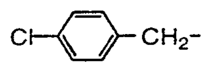
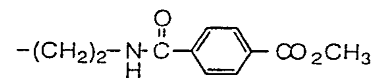
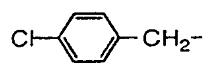
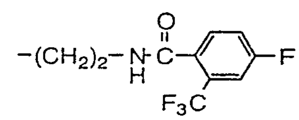
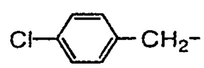
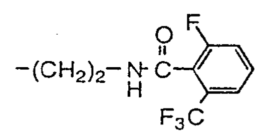
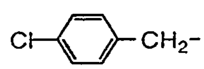
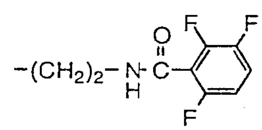
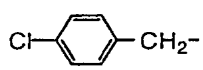
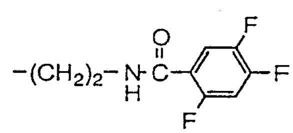
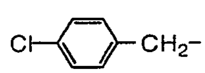
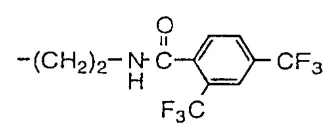
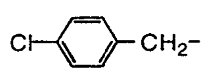
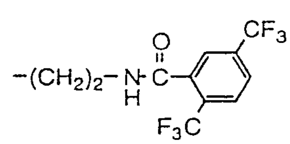
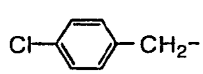
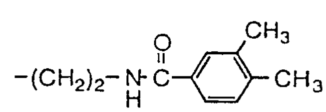
Compd. No.	$R^1(R^2)CH-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
155		1	2	0	R	H	
156		1	2	0	R	H	
157		1	2	0	R	H	
158		1	2	0	R	H	
159		1	2	0	R	H	
160		1	2	0	R	H	
161		1	2	0	R	H	
162		1	2	0	R	H	
163		1	2	0	R	H	
164		1	2	0	R	H	
165		1	2	0	R	H	

Table 1.16

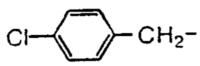
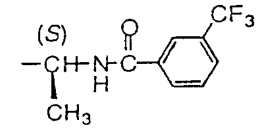
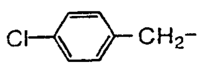
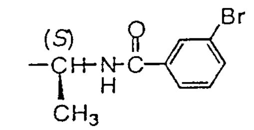
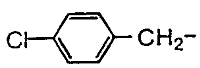
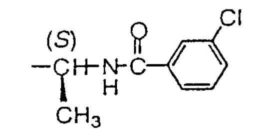
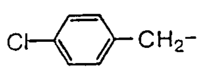
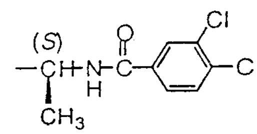
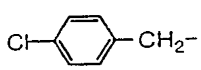
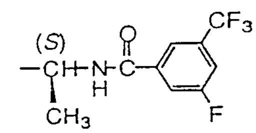
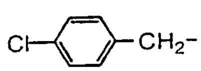
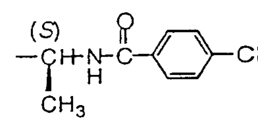
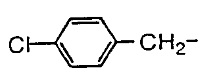
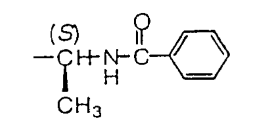
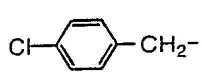
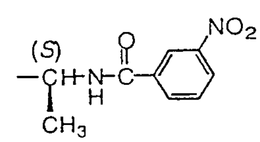
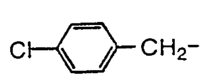
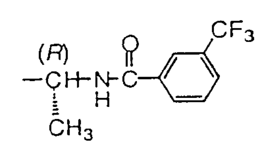
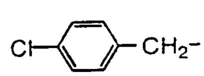
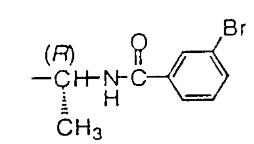
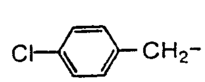
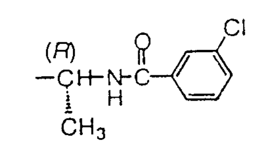
Compd. No.	$R^1$$R^2$>$(CH_2)_j$–	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
166		1	2	0	R	H	
167		1	2	0	R	H	
168		1	2	0	R	H	
169		1	2	0	R	H	
170		1	2	0	R	H	
171		1	2	0	R	H	
172		1	2	0	R	H	
173		1	2	0	R	H	
174		1	2	0	R	H	
175		1	2	0	R	H	
176		1	2	0	R	H	

Table 1.17

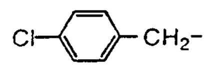
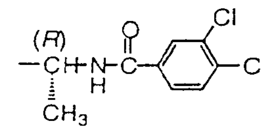
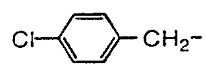
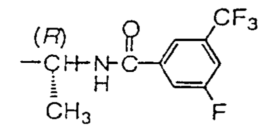
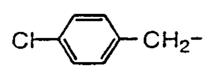
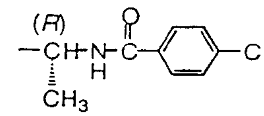
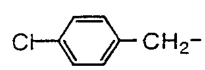
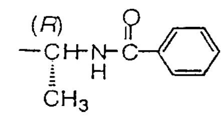
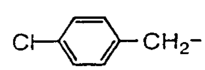
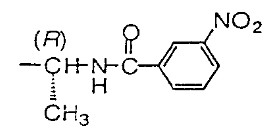
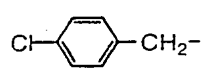
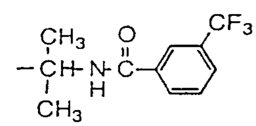
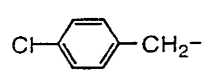
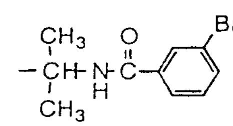
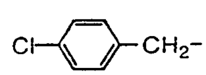
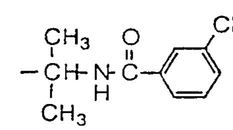
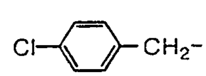
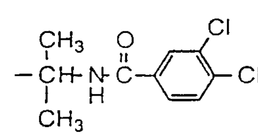
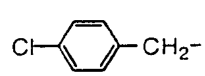
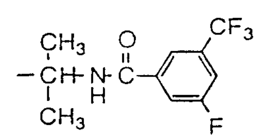
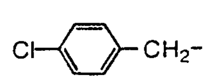
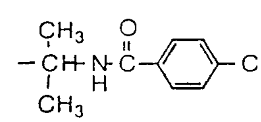
Compd. No.	R^1R^2>-$(CH_2)_j$–	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
177		1	2	0	R	H	
178		1	2	0	R	H	
179		1	2	0	R	H	
180		1	2	0	R	H	
181		1	2	0	R	H	
182		1	2	0	R	H	
183		1	2	0	R	H	
184		1	2	0	R	H	
185		1	2	0	R	H	
186		1	2	0	R	H	
187		1	2	0	R	H	

Table 1.18

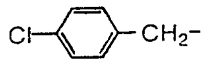
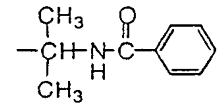
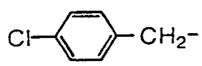
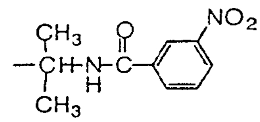
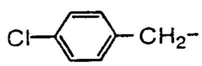
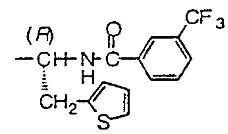
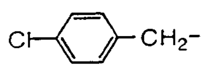
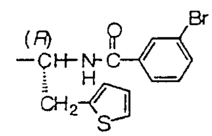
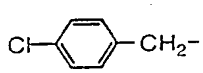
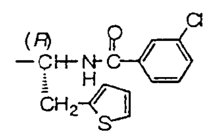
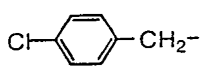
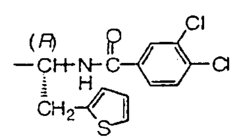
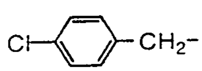
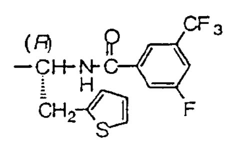
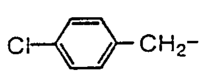
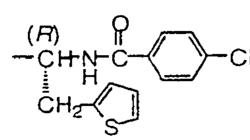
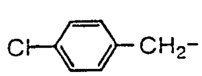
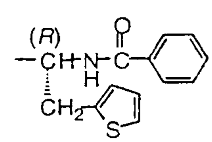
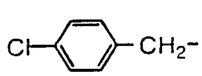
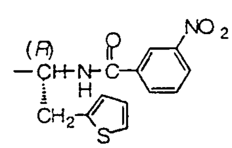
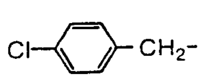
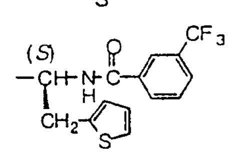
Compd. No.	$R^1R^2>$–$(CH_2)_j$–	k	m	n	chirality	R^3	–$(CH_2)_p$–$C(R^4)(R^5)$–$(CH_2)_q$–G–R^6
188		1	2	0	R	H	
189		1	2	0	R	H	
190		1	2	0	R	H	
191		1	2	0	R	H	
192		1	2	0	R	H	
193		1	2	0	R	H	
194		1	2	0	R	H	
195		1	2	0	R	H	
196		1	2	0	R	H	
197		1	2	0	R	H	
198		1	2	0	R	H	

Table 1.19

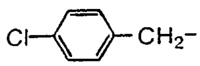
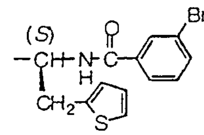
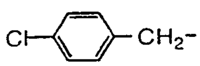
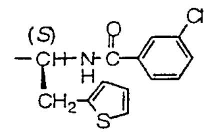
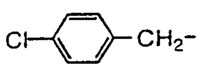
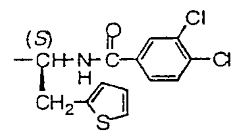
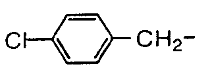
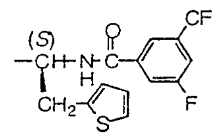
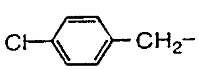
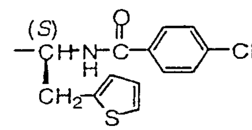
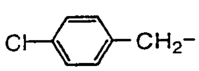
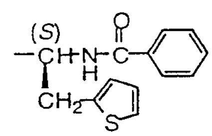
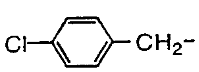
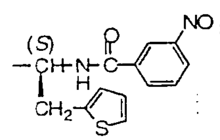
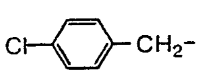
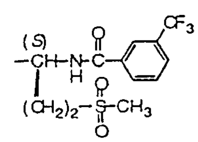
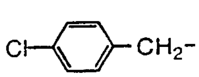
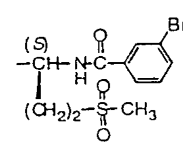
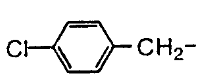
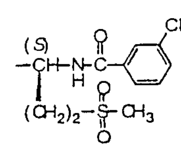
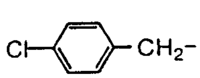
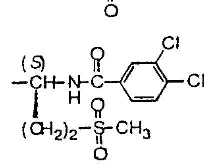
Compd. No.	$R^1R^2>-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
199		1	2	0	R	H	
200		1	2	0	R	H	
201		1	2	0	R	H	
202		1	2	0	R	H	
203		1	2	0	R	H	
204		1	2	0	R	H	
205		1	2	0	R	H	
206		1	2	0	R	H	
207		1	2	0	R	H	
208		1	2	0	R	H	
209		1	2	0	R	H	

Table 1.20

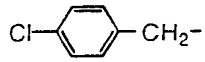
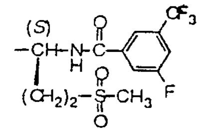
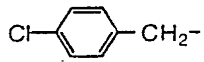
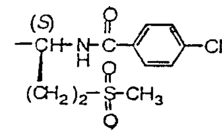
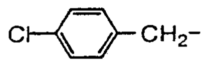
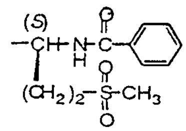
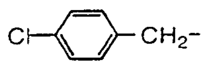
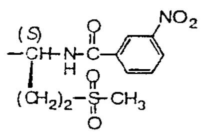
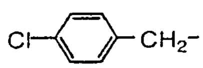
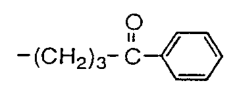
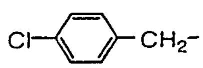
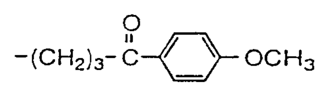
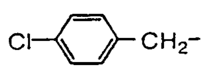
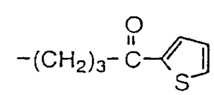
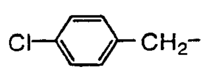
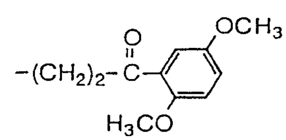
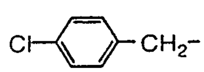
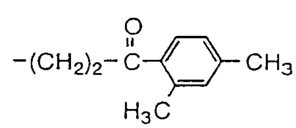
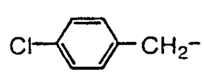
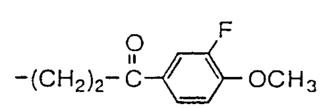
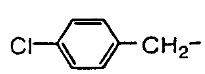
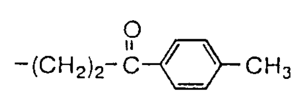
Compd. No.	$R^1R^2CH-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
210		1	2	0	R	H	
211		1	2	0	R	H	
212		1	2	0	R	H	
213		1	2	0	R	H	
214		1	2	0	-	H	
215		1	2	0	-	H	
216		1	2	0	-	H	
217		1	2	0	-	H	
218		1	2	0	-	H	
219		1	2	0	-	H	
220		1	2	0	-	H	

Table 1.21

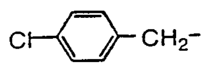
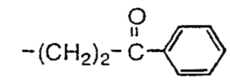
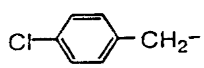
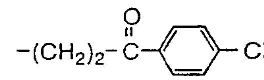
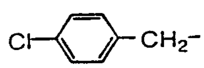
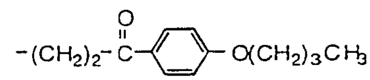
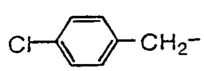
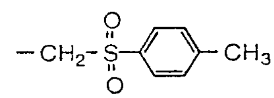
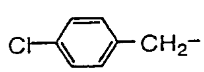
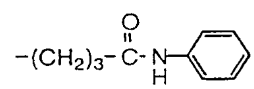
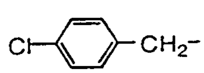
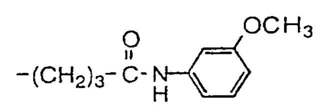
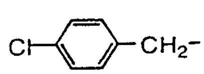
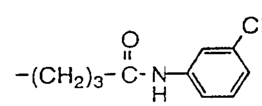
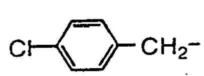
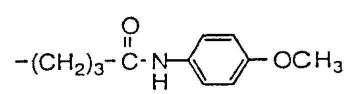
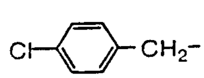
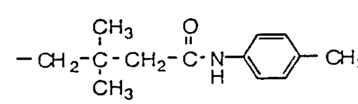
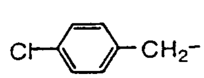
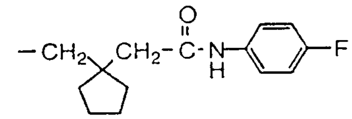
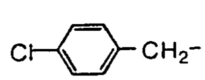
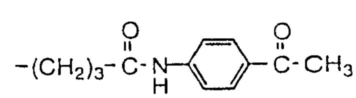
Compd. No.	R^1R^2>$-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
221		1	2	0	-	H	
222		1	2	0	-	H	
223		1	2	0	-	H	
224		1	2	0	-	H	
225		1	2	0	-	H	
226		1	2	0	-	H	
227		1	2	0	-	H	
228		1	2	0	-	H	
229		1	2	0	-	H	
230		1	2	0	-	H	
231		1	2	0	-	H	

Table 1.22

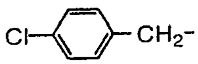
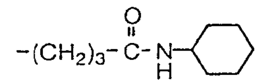
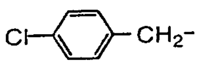
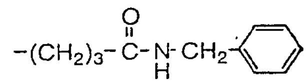
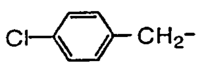
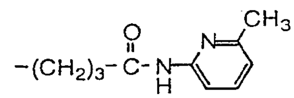
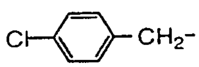
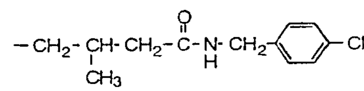
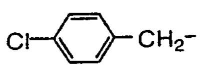
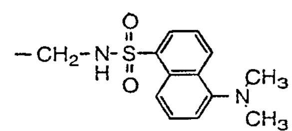
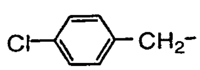
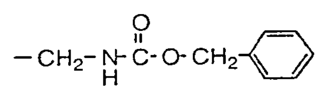
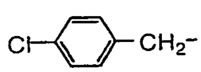
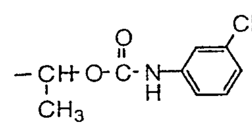
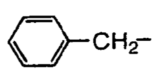
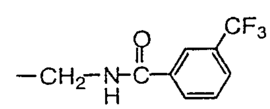
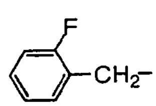
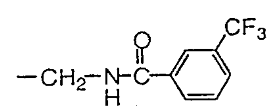
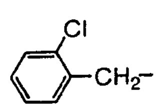
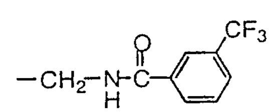
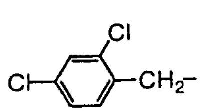
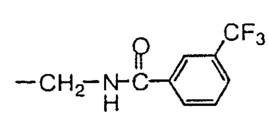
Compd. No.	$R^1R^2>$—$(CH_2)_j$—	k	m	n	chirality	R^3	—$(CH_2)_p$—$C(R^4)(R^5)$—$(CH_2)_q$—G—R^6
232		1	2	0	-	H	
233		1	2	0	-	H	
234		1	2	0	-	H	
235		1	2	0	-	H	
236		1	2	0	-	H	
237		1	2	0	-	H	
238		1	2	0	-	H	
239		1	2	0	S	H	
240		1	2	0	S	H	
241		1	2	0	S	H	
242		1	2	0	S	H	

Table 1.23

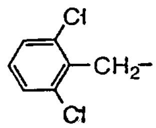
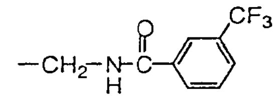
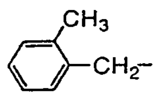
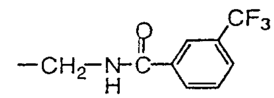
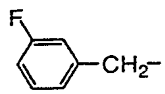
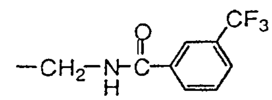
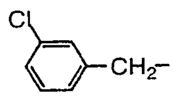
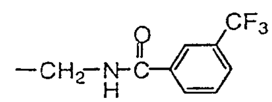
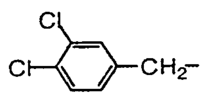
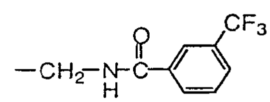
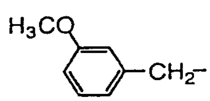
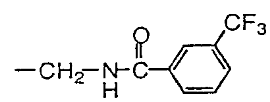
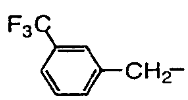
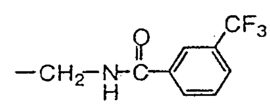
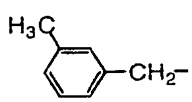
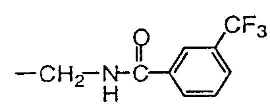
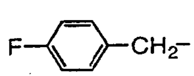
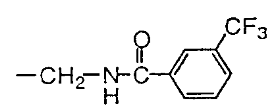
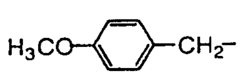
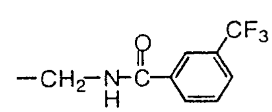
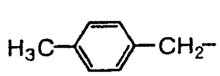
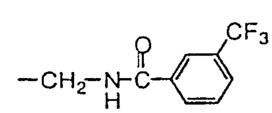
Compd. No.	$R^1R^2>$—$(CH_2)_j$—	k	m	n	chirality	R^3	—$(CH_2)_p$—$C(R^4)(R^5)$—$(CH_2)_q$—G—R^6
243		1	2	0	S	H	
244		1	2	0	S	H	
245		1	2	0	S	H	
246		1	2	0	S	H	
247		1	2	0	S	H	
248		1	2	0	S	H	
249		1	2	0	S	H	
250		1	2	0	S	H	
251		1	2	0	S	H	
252		1	2	0	S	H	
253		1	2	0	S	H	

Table 1.24

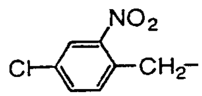
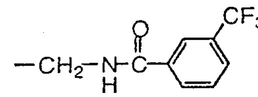
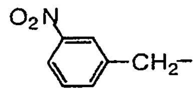
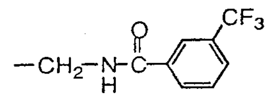
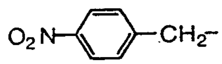
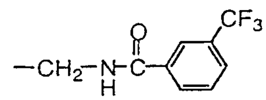
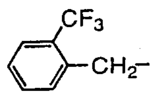
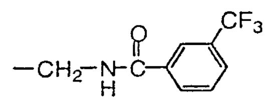
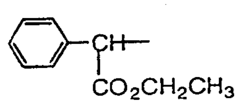
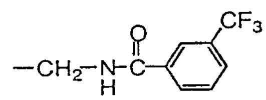
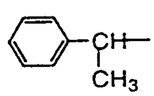
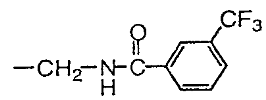
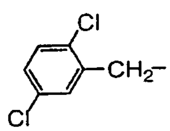
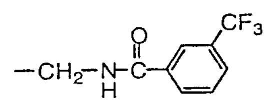
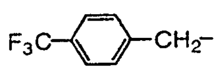
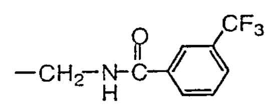
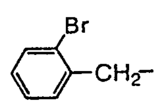
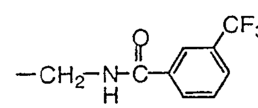
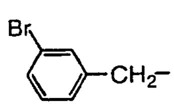
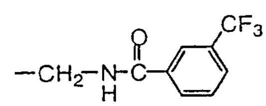
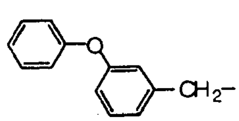
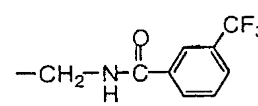
Compd. No.	R^1R^2>$-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
254		1	2	0	S	H	
255		1	2	0	S	H	
256		1	2	0	S	H	
257		1	2	0	S	H	
258		1	2	0	S	H	
259		1	2	0	S	H	
260		1	2	0	S	H	
261		1	2	0	S	H	
262		1	2	0	S	H	
263		1	2	0	S	H	
264		1	2	0	S	H	

Table 1.25

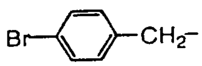
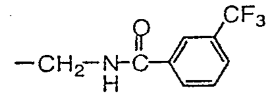
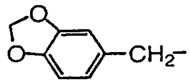
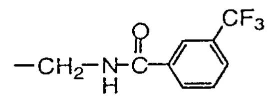
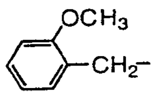
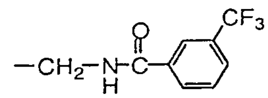
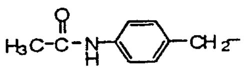
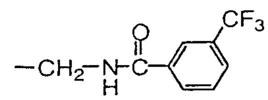
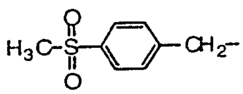
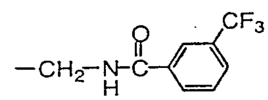
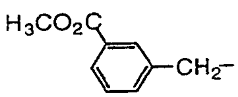
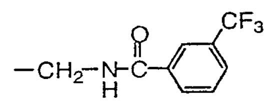
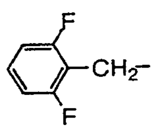
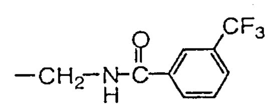
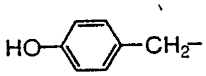
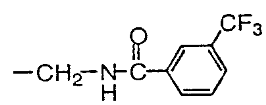
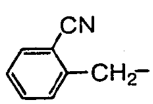
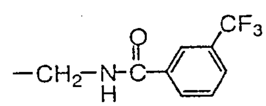
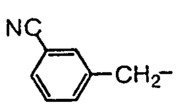
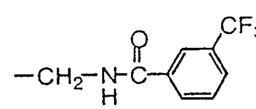
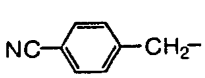
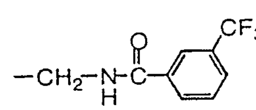
Compd. No.	R^1, R^2 $>$–$(CH_2)_j$–	k	m	n	chirality	R^3	–$(CH_2)_p$–$C(R^4)(R^5)$–$(CH_2)_q$–G–R^6
265		1	2	0	S	H	
266		1	2	0	S	H	
267		1	2	0	S	H	
268		1	2	0	S	H	
269		1	2	0	S	H	
270		1	2	0	S	H	
271		1	2	0	S	H	
272		1	2	0	S	H	
273		1	2	0	S	H	
274		1	2	0	S	H	
275		1	2	0	S	H	

Table 1.26

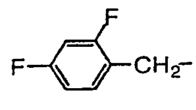
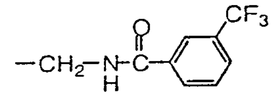
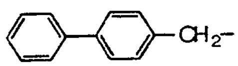
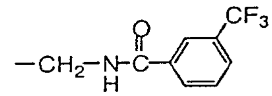
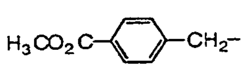
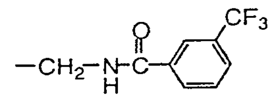
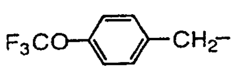
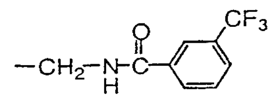
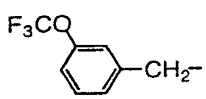
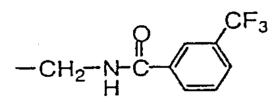
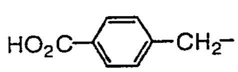
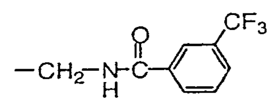
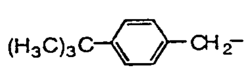
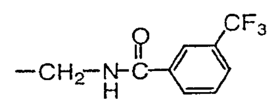
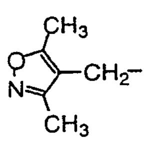
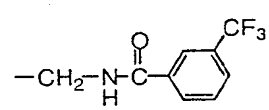
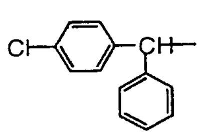
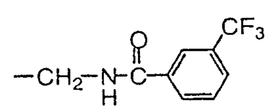
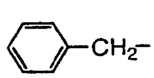
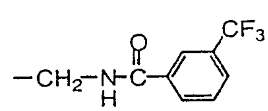
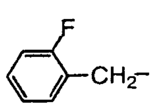
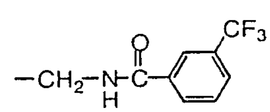
Compd. No.	$R^1R^2>-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
276		1	2	0	S	H	
277		1	2	0	S	H	
278		1	2	0	S	H	
279		1	2	0	S	H	
280		1	2	0	S	H	
281		1	2	0	S	H	
282		1	2	0	S	H	
283		1	2	0	S	H	
284		1	2	0	S	H	
285		1	2	0	R	H	
286		1	2	0	R	H	

Table 1.27

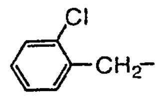
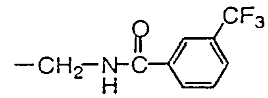
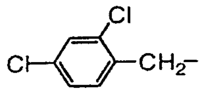
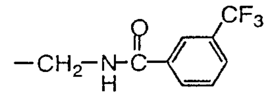
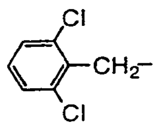
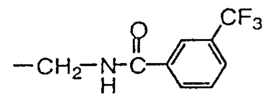
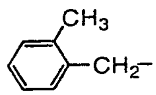
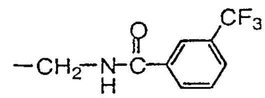
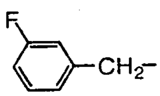
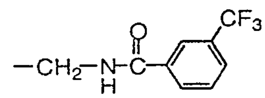
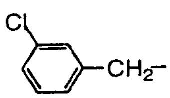
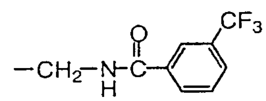
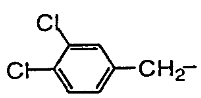
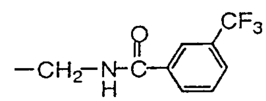
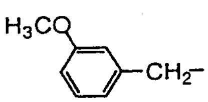
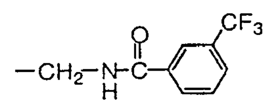
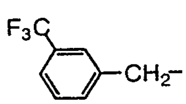
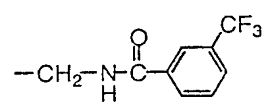
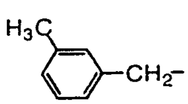
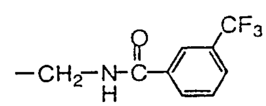
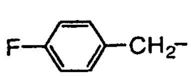
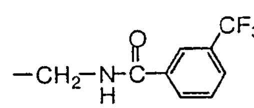
Compd. No.	$\begin{matrix}R^1\\R^2\end{matrix}\!\!>\!-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-\overset{R^4}{\underset{R^5}{C}}-(CH_2)_q-G-R^6$
287		1	2	0	R	H	
288		1	2	0	R	H	
289		1	2	0	R	H	
290		1	2	0	R	H	
291		1	2	0	R	H	
292		1	2	0	R	H	
293		1	2	0	R	H	
294		1	2	0	R	H	
295		1	2	0	R	H	
296		1	2	0	R	H	
297		1	2	0	R	H	

Table 1.28

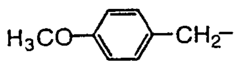
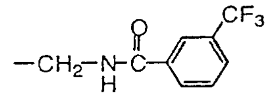
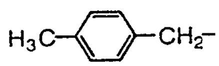
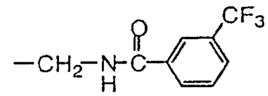
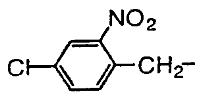
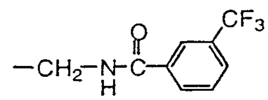
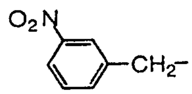
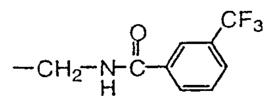
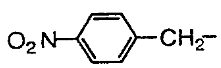
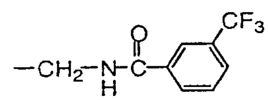
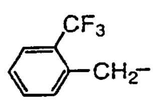
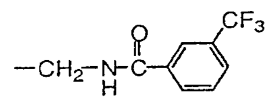
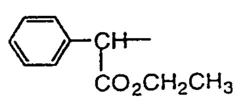
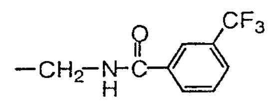
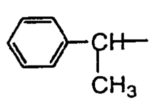
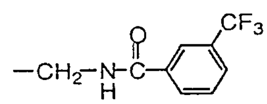
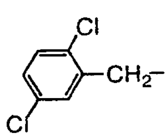
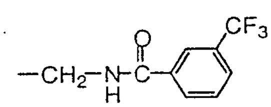
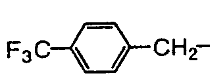
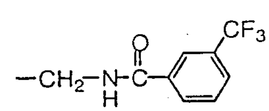
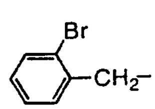
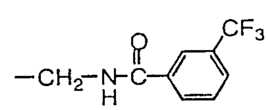
Compd. No.	$R^1R^2>(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
298		1	2	0	R	H	
299		1	2	0	R	H	
300		1	2	0	R	H	
301		1	2	0	R	H	
302		1	2	0	R	H	
303		1	2	0	R	H	
304		1	2	0	R	H	
305		1	2	0	R	H	
306		1	2	0	R	H	
307		1	2	0	R	H	
308		1	2	0	R	H	

Table 1.29

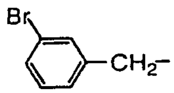
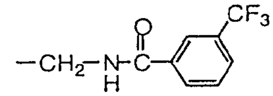
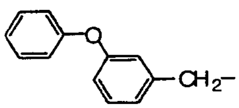
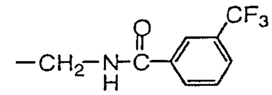
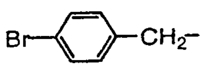
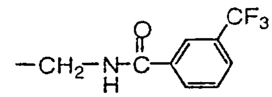
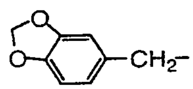
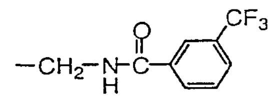
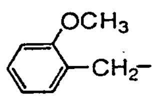
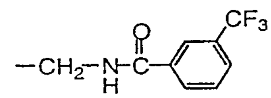
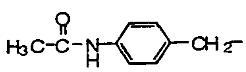
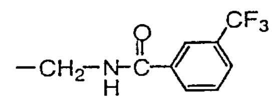
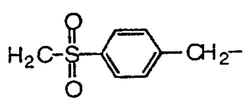
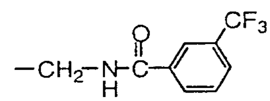
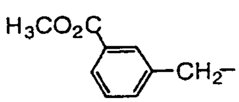
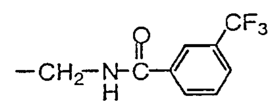
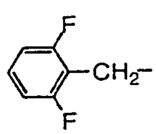
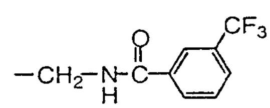
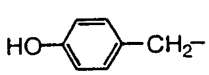
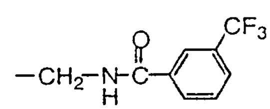
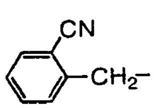
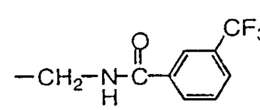
Compd. No.	R^1R^2>$-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
309		1	2	0	R	H	
310		1	2	0	R	H	
311		1	2	0	R	H	
312		1	2	0	R	H	
313		1	2	0	R	H	
314		1	2	0	R	H	
315		1	2	0	R	H	
316		1	2	0	R	H	
317		1	2	0	R	H	
318		1	2	0	R	H	
319		1	2	0	R	H	

Table 1.30

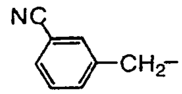
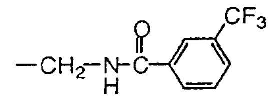
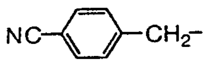
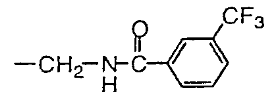
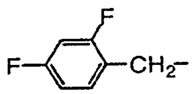
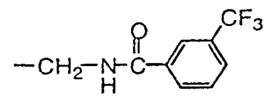
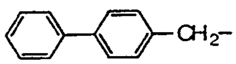
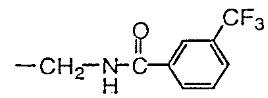
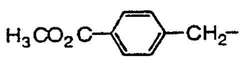
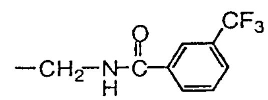
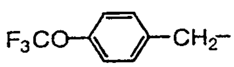
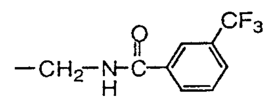
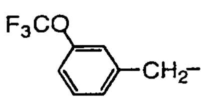
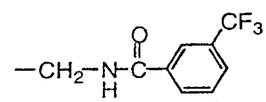
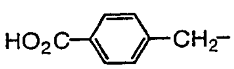
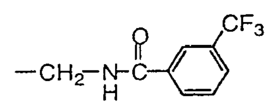
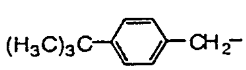
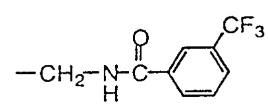
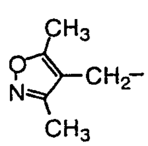
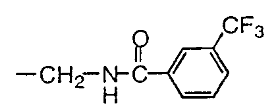
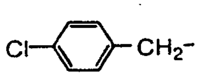
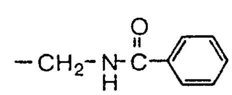
Compd. No.	R^1R^2>$-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
320		1	2	0	R	H	
321		1	2	0	R	H	
322		1	2	0	R	H	
323		1	2	0	R	H	
324		1	2	0	R	H	
325		1	2	0	R	H	
326		1	2	0	R	H	
327		1	2	0	R	H	
328		1	2	0	R	H	
329		1	2	0	R	H	
330		0	3	1	-	H	

Table 1.31

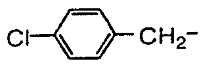
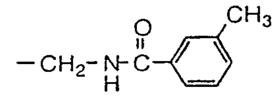
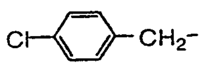
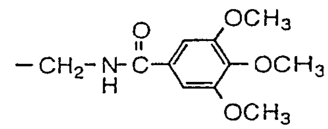
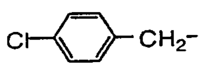
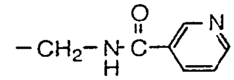
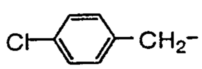
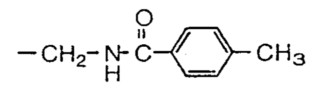
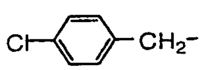
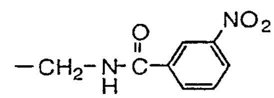
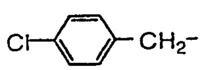
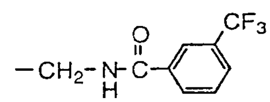
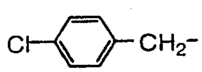
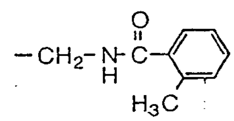
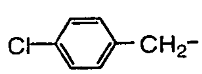
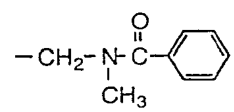
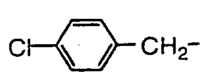
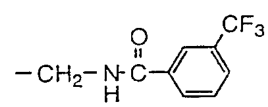
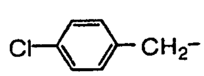
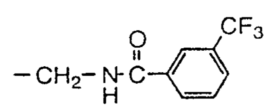
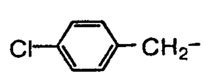
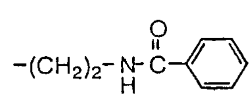
Compd. No.	$R^1R^2{>}(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
331		0	3	1	-	H	
332		0	3	1	-	H	
333		0	3	1	-	H	
334		0	3	1	-	H	
335		0	3	1	-	H	
336		0	3	1	-	H	
337		0	3	1	-	H	
338		0	3	1	-	H	
339		0	3	1	R	H	
340		0	3	1	S	H	
341		0	3	1	-	H	

Table 1.32

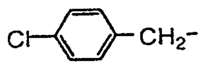
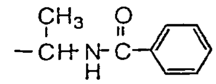
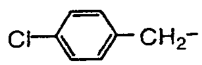
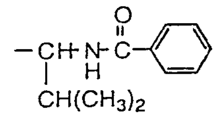
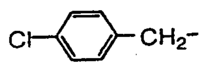
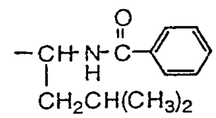
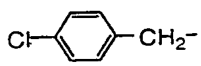
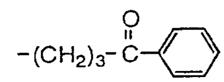
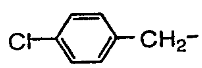
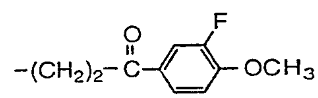
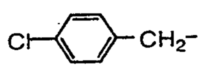
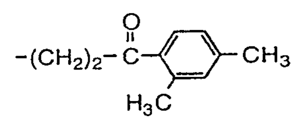
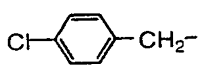
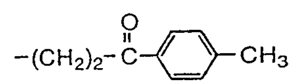
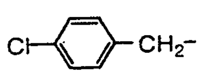
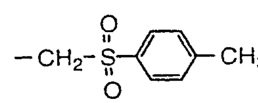
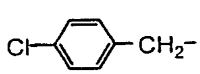
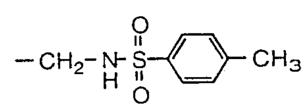
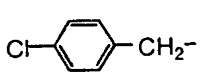
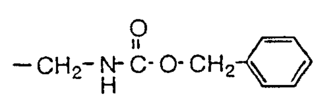
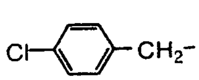
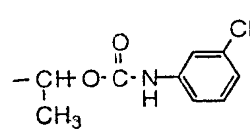
Compd. No.	$R^1R^2>$-$(CH_2)_j$-	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
342		0	3	1	-	H	
343		0	3	1	-	H	
344		0	3	1	-	H	
345		0	3	1	-	H	
346		0	3	1	-	H	
347		0	3	1	-	H	
348		0	3	1	-	H	
349		0	3	1	-	H	
350		0	3	1	-	H	
351		0	3	1	-	H	
352		0	3	1	-	H	

Table 1.33

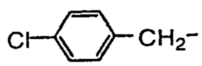
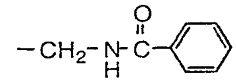
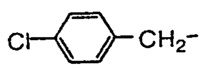
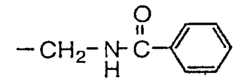
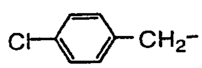
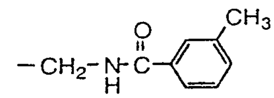
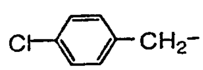
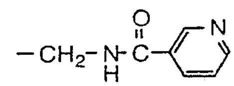
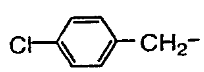
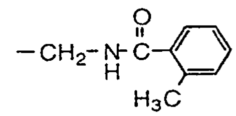
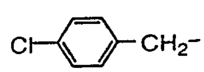
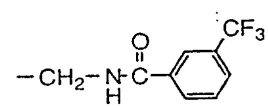
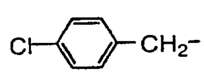
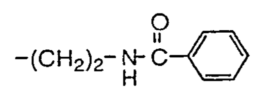
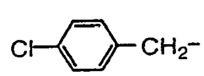
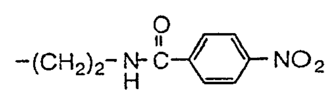
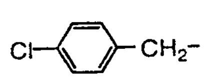
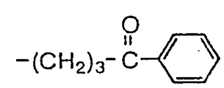
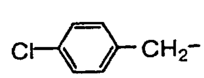
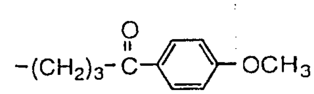
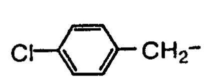
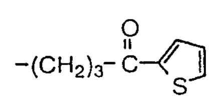
Compd. No.	$R^1R^2{>}\!-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
353		1	2	1	-	H	
354		1	3	0	-	H	
355		1	3	0	-	H	
356		1	3	0	-	H	
357		1	3	0	-	H	
358		1	3	0	-	H	
359		1	3	0	-	H	
360		1	3	0	-	H	
361		1	3	0	-	H	
362		1	3	0	-	H	
363		1	3	0	-	H	

Table 1.34

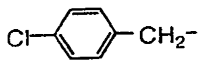
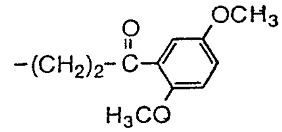
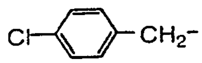
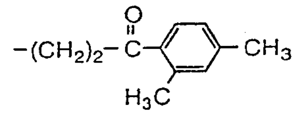
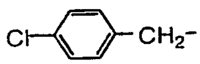
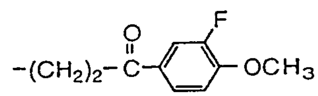
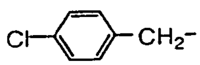
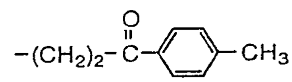
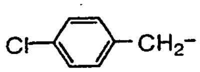
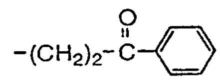
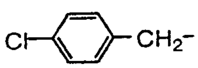
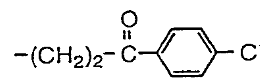
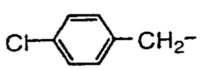
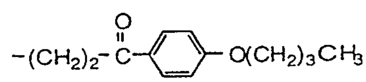
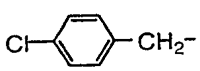
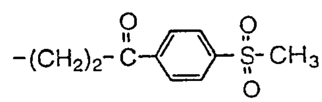
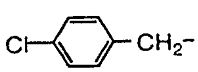
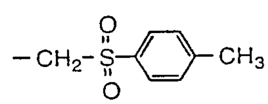
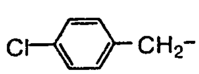
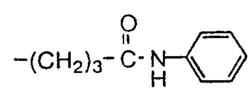
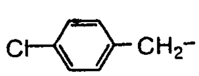
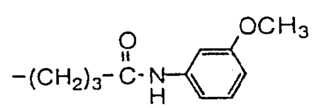
Compd. No.	$R^1R^2>-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
364		1	3	0	-	H	
365		1	3	0	-	H	
366		1	3	0	-	H	
367		1	3	0	-	H	
368		1	3	0	-	H	
369		1	3	0	-	H	
370		1	3	0	-	H	
371		1	3	0	-	H	
372		1	3	0	-	H	
373		1	3	0	-	H	
374		1	3	0	-	H	

Table 1.35

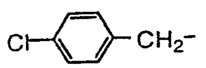
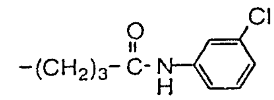
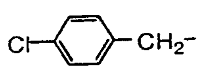
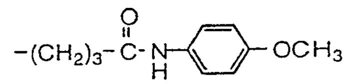
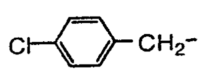
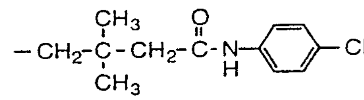
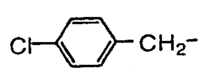
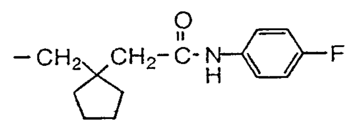
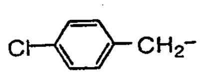
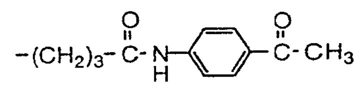
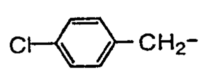
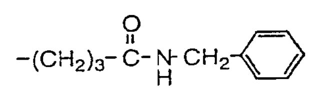
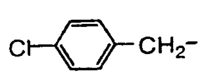
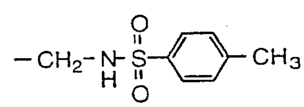
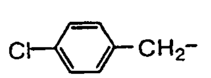
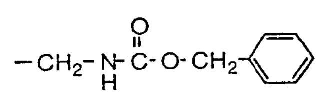
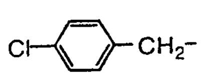
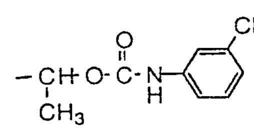
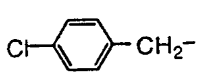
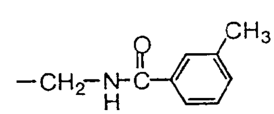
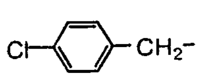
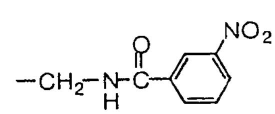
Compd. No.	R^1R^2>$(CH_2)_j$–	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
375		1	3	0	-	H	
376		1	3	0	-	H	
377		1	3	0	-	H	
378		1	3	0	-	H	
379		1	3	0	-	H	
380		1	3	0	-	H	
381		1	3	0	-	H	
382		1	3	0	-	H	
383		1	3	0	-	H	
384		2	2	0	-	H	
385		2	2	0	-	H	

Table 1.36

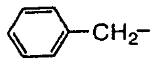
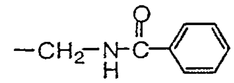
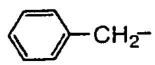
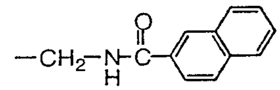
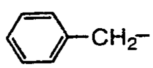
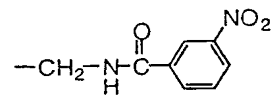
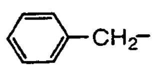
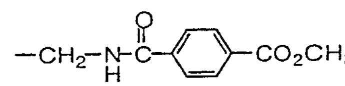
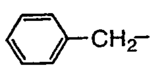
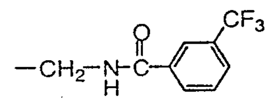
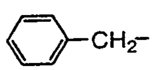
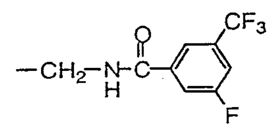
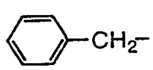
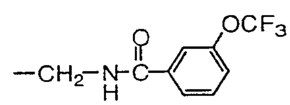
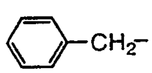
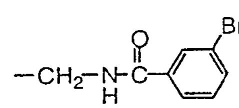
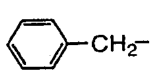
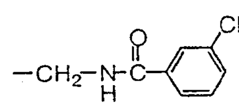
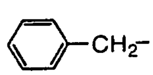
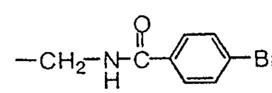
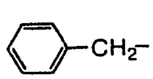
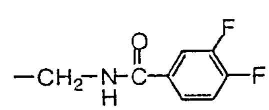
Compd. No.	R^1R^2>-$(CH_2)_j$–	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
386		2	2	0	-	H	
387		2	2	0	-	H	
388		2	2	0	-	H	
389		2	2	0	-	H	
390		2	2	0	-	H	
391		2	2	0	-	H	
392		2	2	0	-	H	
393		2	2	0	-	H	
394		2	2	0	-	H	
395		2	2	0	-	H	
396		2	2	0	-	H	

Table 1.37

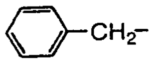
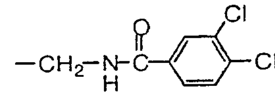
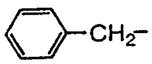
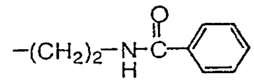
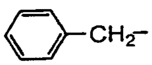
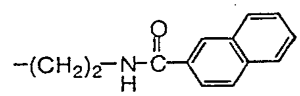
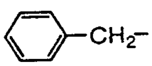
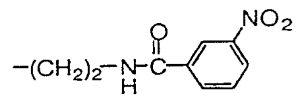
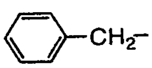
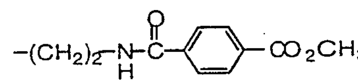
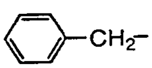
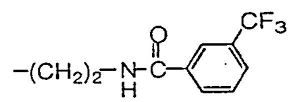
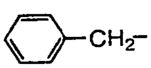
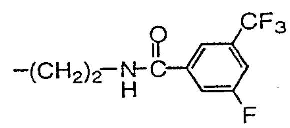
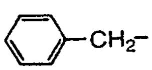
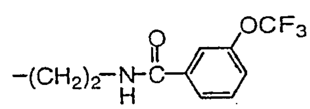
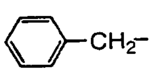
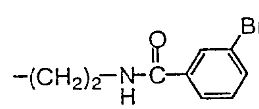
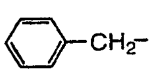
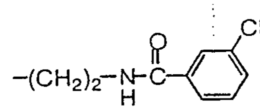
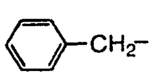
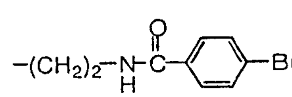
Compd. No.	$R^1R^2>-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-\overset{R^4}{\underset{R^5}{C}}-(CH_2)_q-G-R^6$
397		2	2	0	-	H	
398		2	2	0	-	H	
399		2	2	0	-	H	
400		2	2	0	-	H	
401		2	2	0	-	H	
402		2	2	0	-	H	
403		2	2	0	-	H	
404		2	2	0	-	H	
405		2	2	0	-	H	
406		2	2	0	-	H	
407		2	2	0	-	H	

Table 1.38

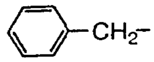
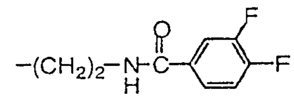
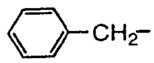
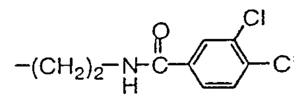
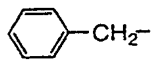
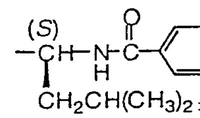
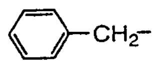
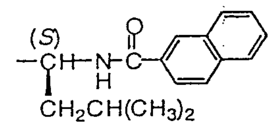
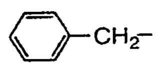
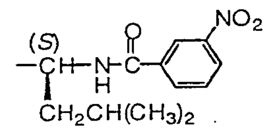
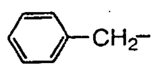
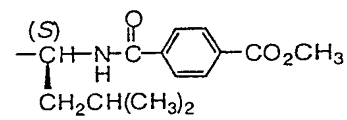
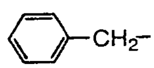
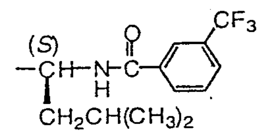
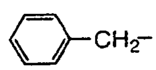
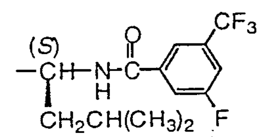
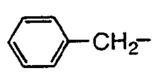
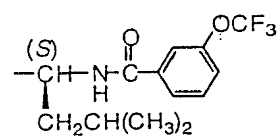
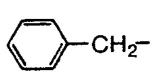
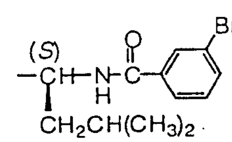
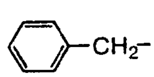
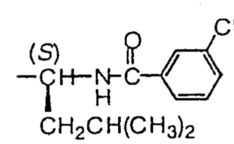
Compd. No.	R^1, R^2 $>$–$(CH_2)_j$–	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
408		2	2	0	-	H	
409		2	2	0	-	H	
410		2	2	0	-	H	
411		2	2	0	-	H	
412		2	2	0	-	H	
413		2	2	0	-	H	
414		2	2	0	-	H	
415		2	2	0	-	H	
416		2	2	0	-	H	
417		2	2	0	-	H	
418		2	2	0	-	H	

Table 1.39

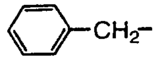
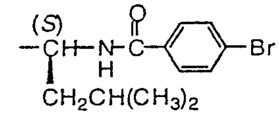
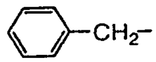
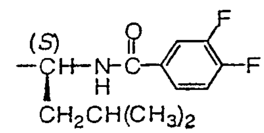
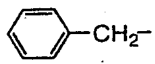
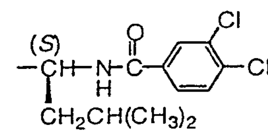
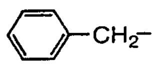
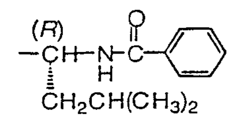
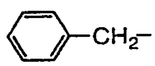
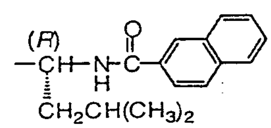
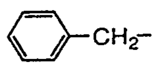
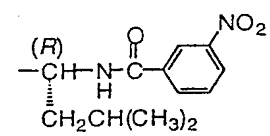
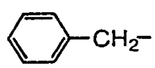
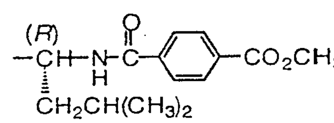
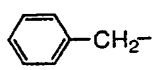
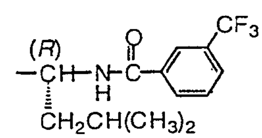
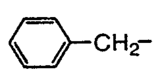
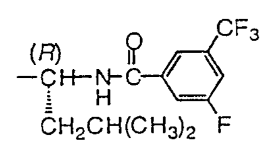
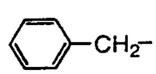
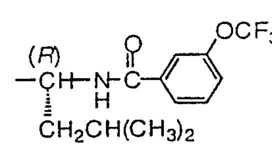
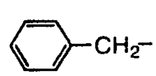
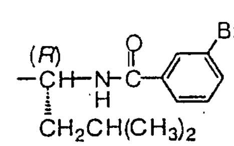
Compd. No.	$R^1R^2>$$-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
419		2	2	0	-	H	
420		2	2	0	-	H	
421		2	2	0	-	H	
422		2	2	0	-	H	
423		2	2	0	-	H	
424		2	2	0	-	H	
425		2	2	0	-	H	
426		2	2	0	-	H	
427		2	2	0	-	H	
428		2	2	0	-	H	
429		2	2	0	-	H	

Table 1.40

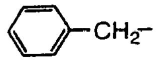
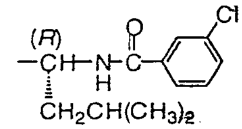
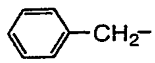
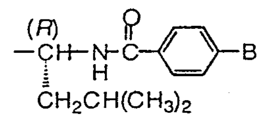
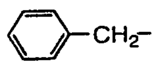
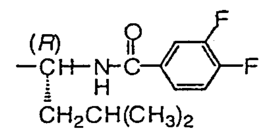
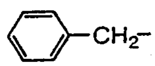
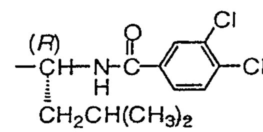
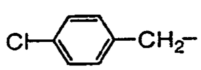
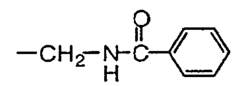
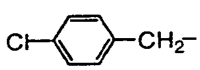
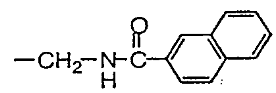
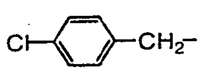
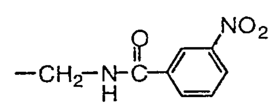
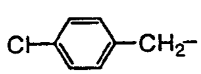
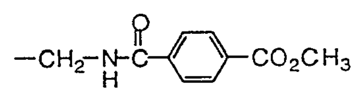
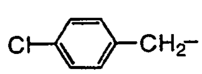
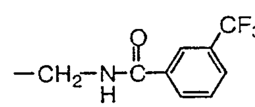
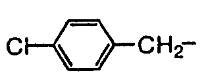
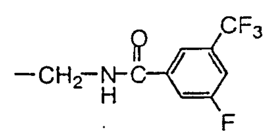
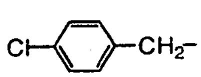
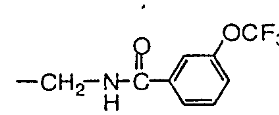
Compd. No.	$R^1R^2C-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
430		2	2	0	-	H	
431		2	2	0	-	H	
432		2	2	0	-	H	
433		2	2	0	-	H	
434		1	3	1	-	H	
435		1	3	1	-	H	
436		1	3	1	-	H	
437		1	3	1	-	H	
438		1	3	1	-	H	
439		1	3	1	-	H	
440		1	3	1	-	H	

Table 1.41

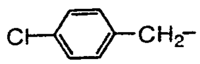
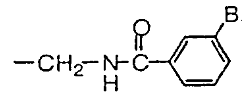
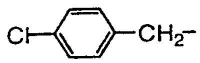
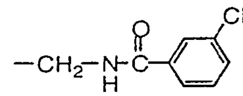
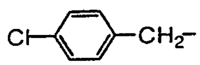
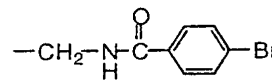
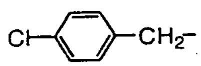
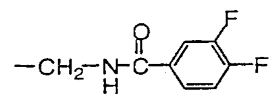
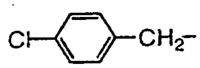
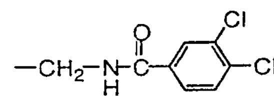
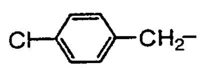
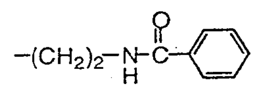
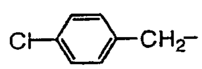
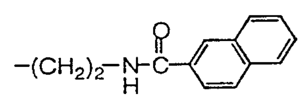
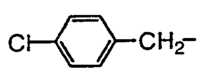
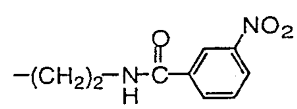
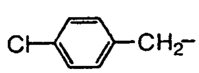
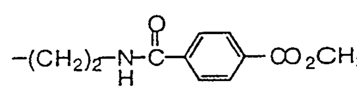
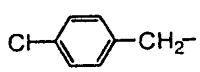
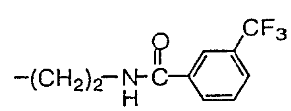
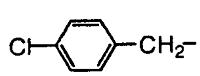
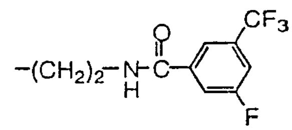
Compd. No.	$R^1R^2>-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
441		1	3	1	-	H	
442		1	3	1	-	H	
443		1	3	1	-	H	
444		1	3	1	-	H	
445		1	3	1	-	H	
446		1	3	1	-	H	
447		1	3	1	-	H	
448		1	3	1	-	H	
449		1	3	1	-	H	
450		1	3	1	-	H	
451		1	3	1	-	H	

Table 1.42

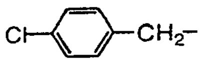
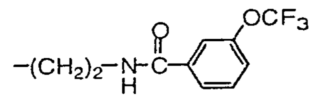
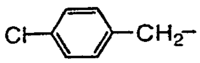
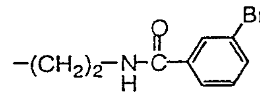
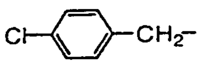
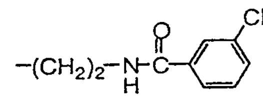
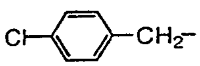
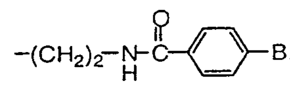
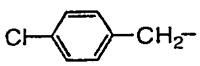
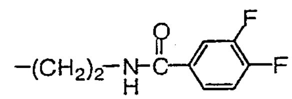
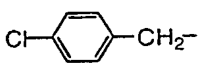
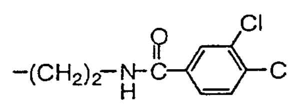
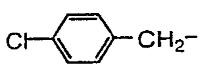
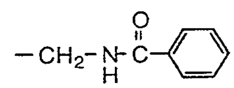
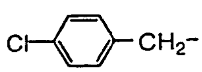
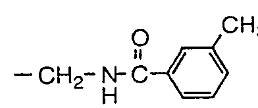
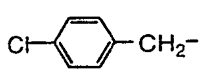
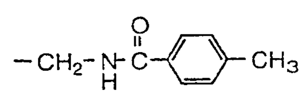
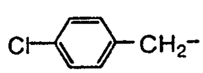
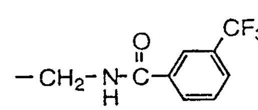
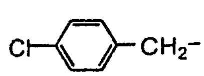
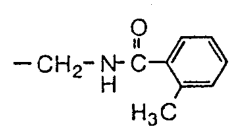
Compd. No.	$R^1R^2>-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
452		1	3	1	-	H	
453		1	3	1	-	H	
454		1	3	1	-	H	
455		1	3	1	-	H	
456		1	3	1	-	H	
457		1	3	1	-	H	
458		2	2	1	-	H	
459		2	2	1	-	H	
460		2	2	1	-	H	
461		2	2	1	-	H	
462		2	2	1	-	H	

Table 1.43

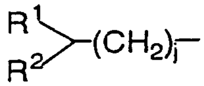
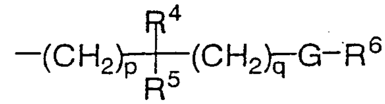
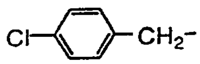
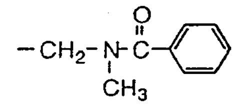
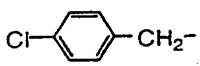
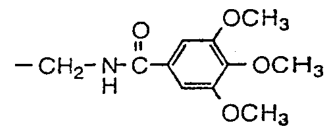
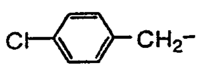
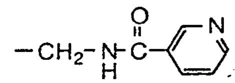
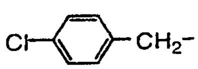
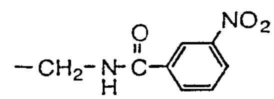
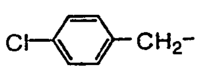
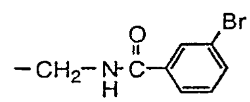
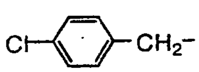
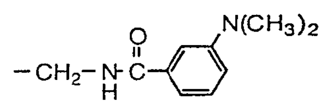
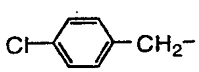
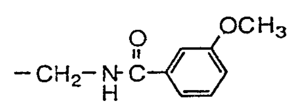
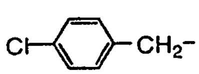
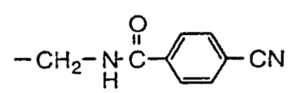
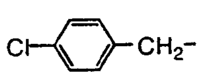
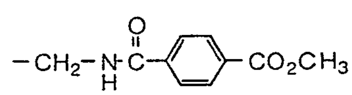
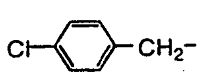
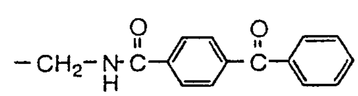
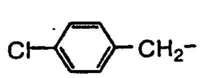
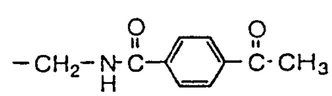
Compd. No.		k	m	n	chirality	R^3	
463		2	2	1	-	H	
464		2	2	1	-	H	
465		2	2	1	-	H	
466		2	2	1	-	H	
467		2	2	1	-	H	
468		2	2	1	-	H	
469		2	2	1	-	H	
470		2	2	1	-	H	
471		2	2	1	-	H	
472		2	2	1	-	H	
473		2	2	1	-	H	

Table 1.44

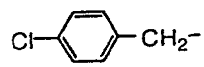
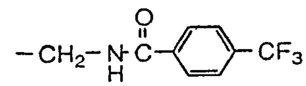
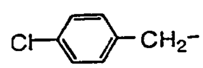
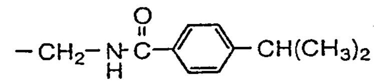
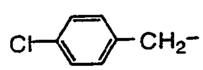
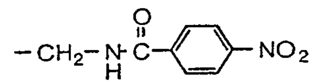
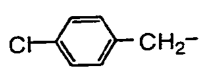
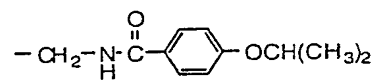
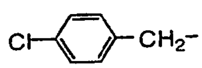
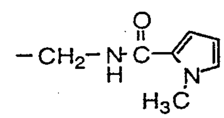
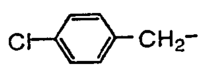
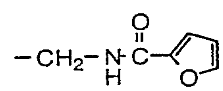
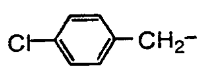
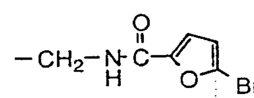
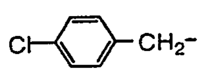
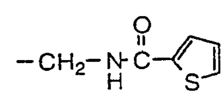
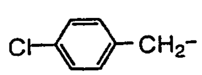
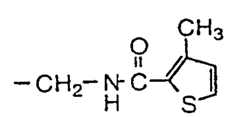
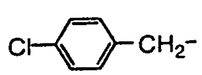
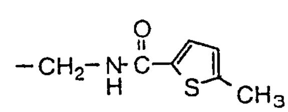
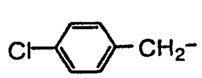
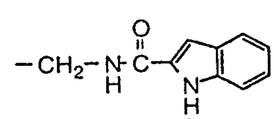
Compd. No.	R^1R^2>-$(CH_2)_j$-	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
474		2	2	1	-	H	
475		2	2	1	-	H	
476		2	2	1	-	H	
477		2	2	1	-	H	
478		2	2	1	-	H	
479		2	2	1	-	H	
480		2	2	1	-	H	
481		2	2	1	-	H	
482		2	2	1	-	H	
483		2	2	1	-	H	
484		2	2	1	-	H	

Table 1.45

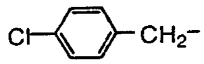
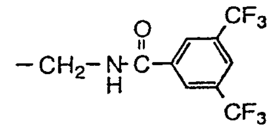
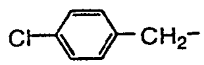
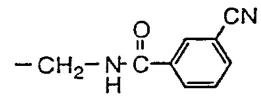
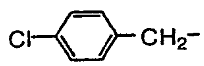
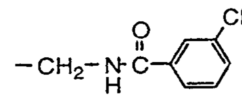
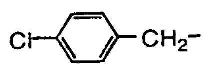
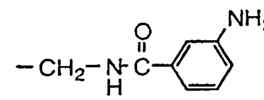
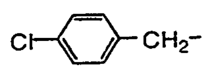
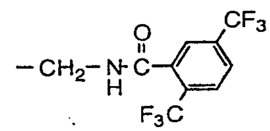
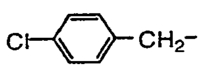
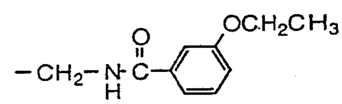
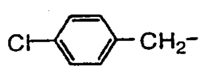
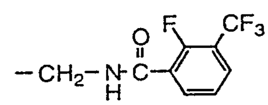
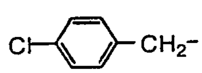
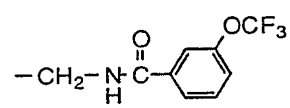
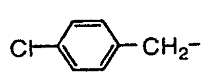
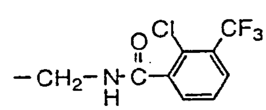
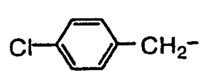
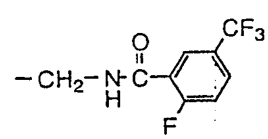
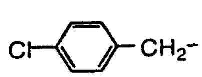
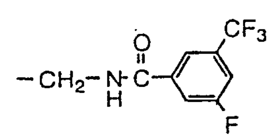
Compd. No.	$R^1R^2{>}(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
485		2	2	1	-	H	
486		2	2	1	-	H	
487		2	2	1	-	H	
488		2	2	1	-	H	
489		2	2	1	-	H	
490		2	2	1	-	H	
491		2	2	1	-	H	
492		2	2	1	-	H	
493		2	2	1	-	H	
494		2	2	1	-	H	
495		2	2	1	-	H	

Table 1.46

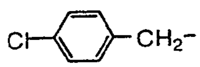
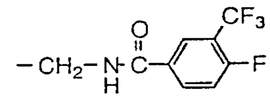
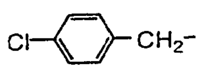
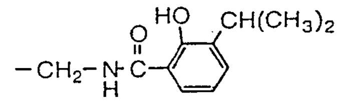
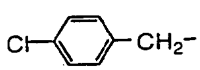
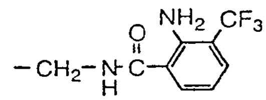
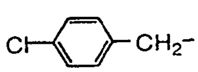
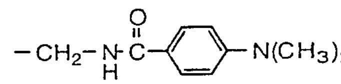
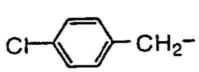
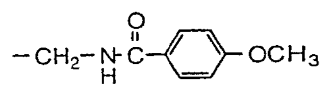
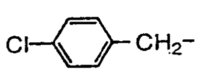
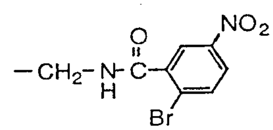
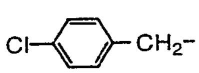
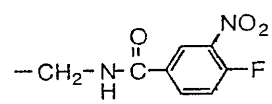
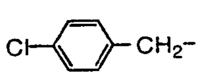
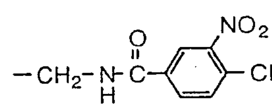
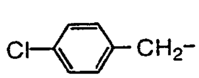
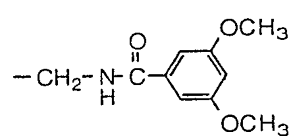
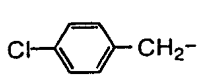
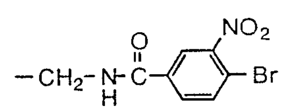
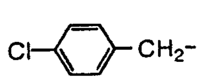
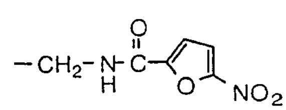
Compd. No.	$R^1R^2>$-$(CH_2)_j$-	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
496		2	2	1	-	H	
497		2	2	1	-	H	
498		2	2	1	-	H	
499		2	2	1	-	H	
500		2	2	1	-	H	
501		2	2	1	-	H	
502		2	2	1	-	H	
503		2	2	1	-	H	
504		2	2	1	-	H	
505		2	2	1	-	H	
506		2	2	1	-	H	

Table 1.47

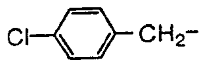
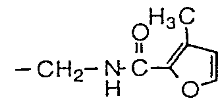
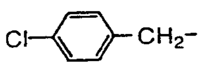
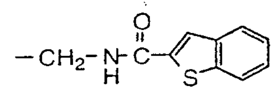
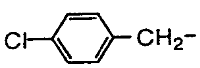
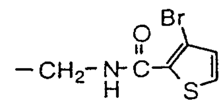
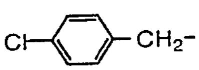
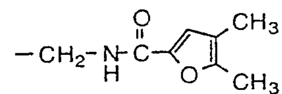
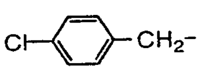
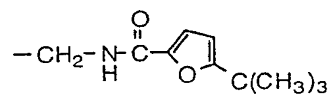
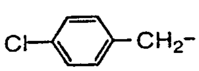
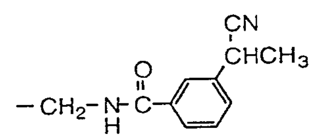
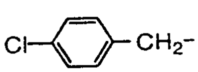
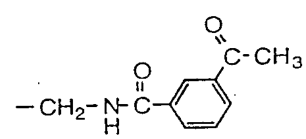
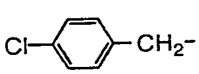
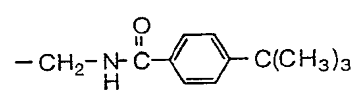
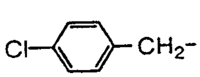
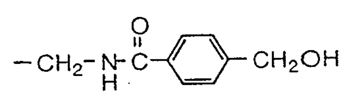
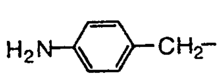
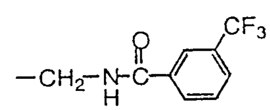
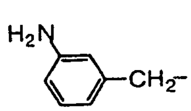
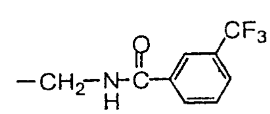
Compd. No.	$R^1R^2>$–$(CH_2)_j$–	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
507		2	2	1	-	H	
508		2	2	1	-	H	
509		2	2	1	-	H	
510		2	2	1	-	H	
511		2	2	1	-	H	
512		2	2	1	-	H	
513		2	2	1	-	H	
514		2	2	1	-	H	
515		2	2	1	-	H	
516		2	2	1	-	H	
517		2	2	1	-	H	

Table 1.48

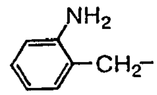
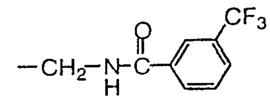
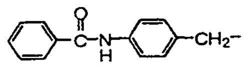
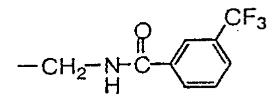
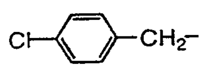
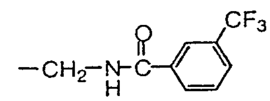
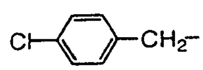
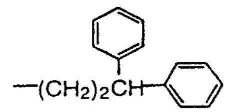
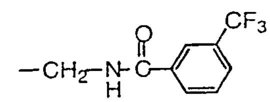
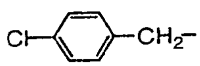
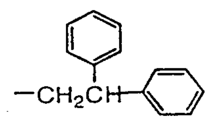
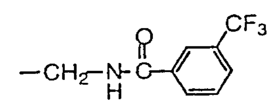
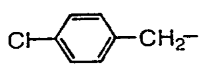
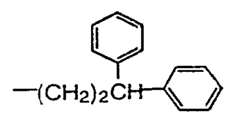
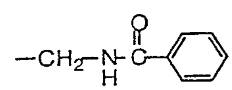
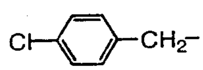
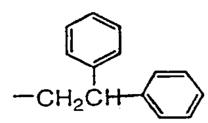
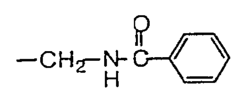
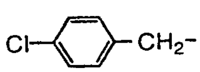
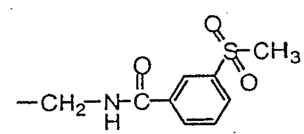
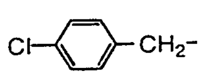
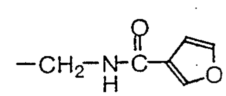
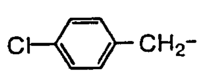
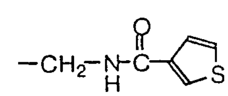
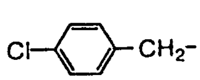
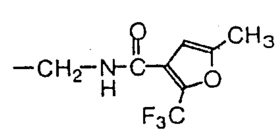
Compd. No.	$R^1R^2>$$-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
518		2	2	1	-	H	
519		2	2	1	-	H	
520		2	2	1	-	$-CH_3$	
521		2	2	1	-		
522		2	2	1	-		
523		2	2	1	-		
524		2	2	1	-		
525		2	2	1	-	H	
526		2	2	1	-	H	
527		2	2	1	-	H	
528		2	2	1	-	H	

Table 1.49

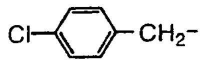
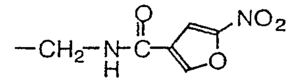
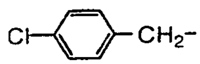
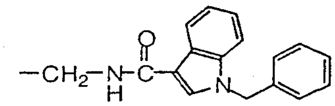
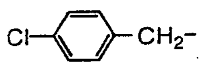
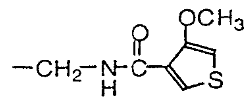
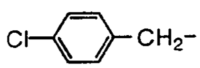
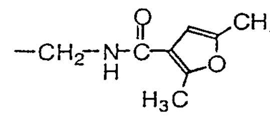
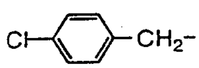
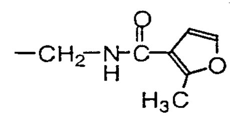
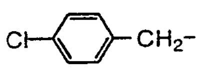
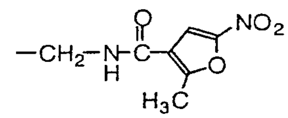
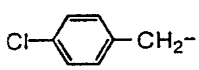
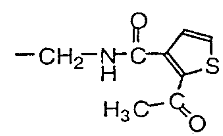
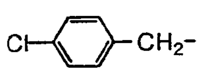
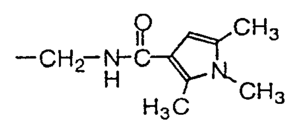
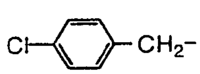
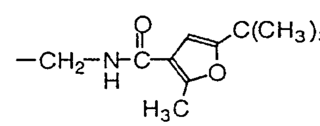
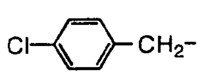
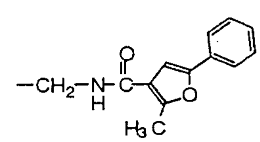
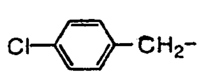
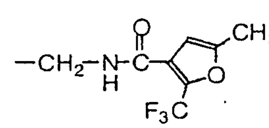
Compd. No.	$R^1R^2>-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
529		2	2	1	-	H	
530		2	2	1	-	H	
531		2	2	1	-	H	
532		2	2	1	-	H	
533		2	2	1	-	H	
534		2	2	1	-	H	
535		2	2	1	-	H	
536		2	2	1	-	H	
537		2	2	1	-	H	
538		2	2	1	-	H	
539		2	2	1	-	H	

Table 1.50

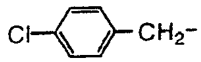
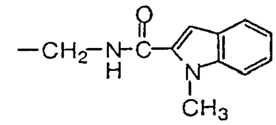
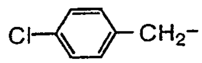
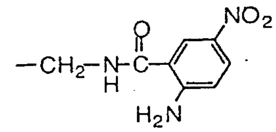
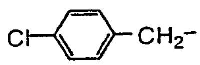
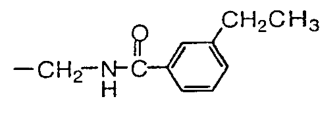
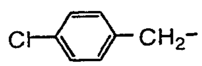
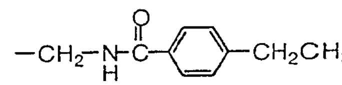
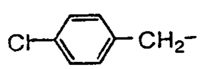
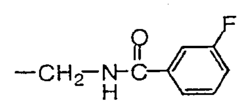
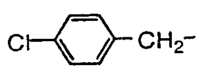
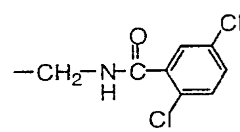
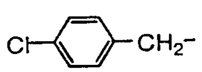
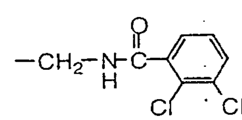
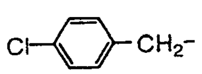
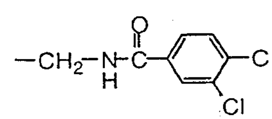
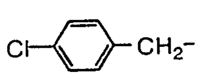
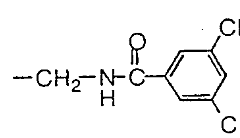
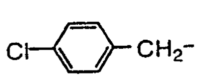
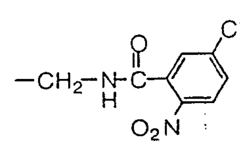
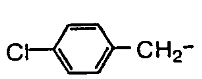
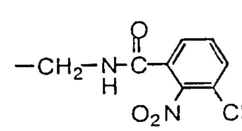
Compd. No.	$R^1R^2>$-$(CH_2)_j$-	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
540		2	2	1	-	H	
541		2	2	1	-	H	
542		2	2	1	-	H	
543		2	2	1	-	H	
544		2	2	1	-	H	
545		2	2	1	-	H	
546		2	2	1	-	H	
547		2	2	1	-	H	
548		2	2	1	-	H	
549		2	2	1	-	H	
550		2	2	1	-	H	

Table 1.51

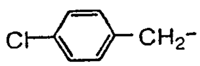
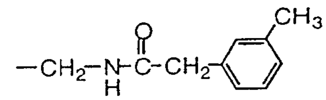
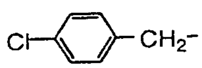
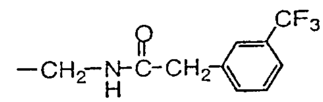
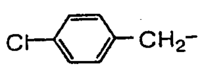
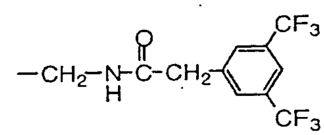
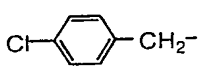
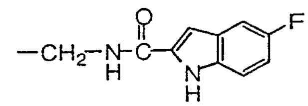
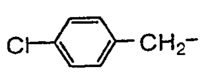
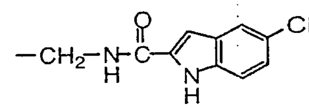
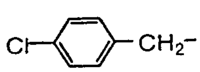
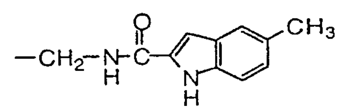
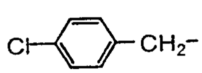
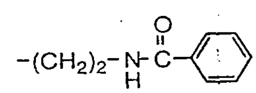
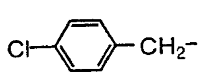
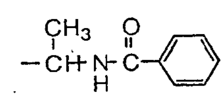
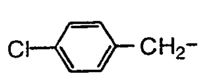
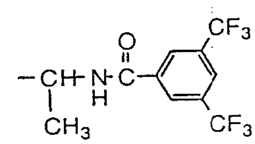
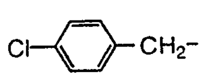
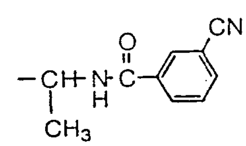
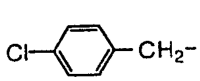
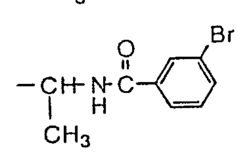
Compd. No.	R^1R^2>-$(CH_2)_j$-	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
551		2	2	1	-	H	
552		2	2	1	-	H	
553		2	2	1	-	H	
554		2	2	1	-	H	
555		2	2	1	-	H	
556		2	2	1	-	H	
557		2	2	1	-	H	
558		2	2	1	-	H	
559		2	2	1	-	H	
560		2	2	1	-	H	
561		2	2	1	-	H	

Table 1.52

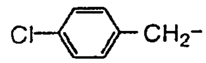
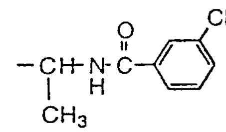
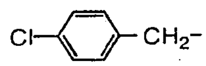
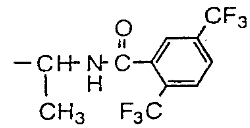
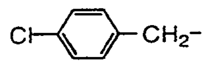
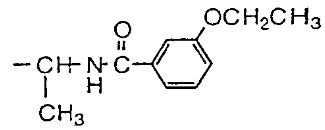
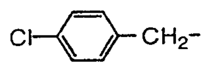
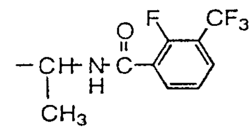
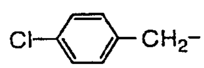
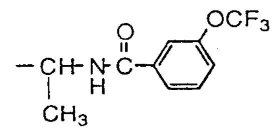
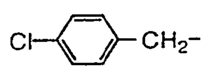
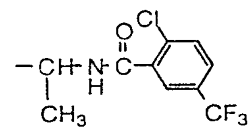
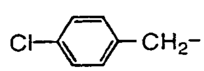
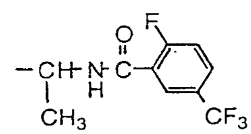
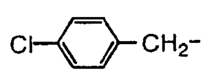
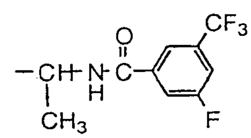
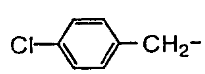
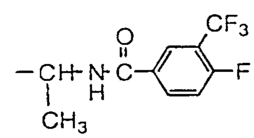
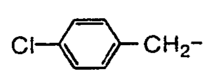
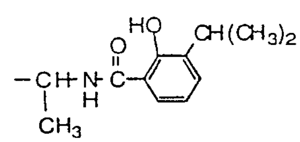
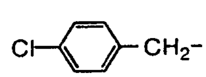
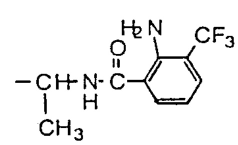
Compd. No.	R^1R^2>-$(CH_2)_j$-	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
562		2	2	1	-	H	
563		2	2	1	-	H	
564		2	2	1	-	H	
565		2	2	1	-	H	
566		2	2	1	-	H	
567		2	2	1	-	H	
568		2	2	1	-	H	
569		2	2	1	-	H	
570		2	2	1	-	H	
571		2	2	1	-	H	
572		2	2	1	-	H	

Table 1.53

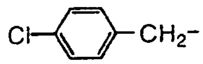
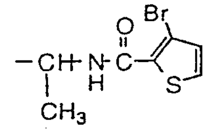
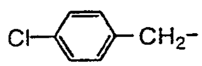
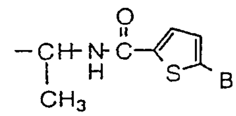
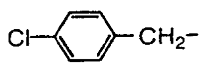
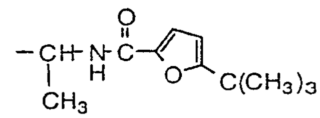
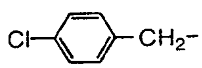
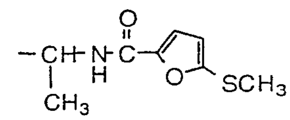
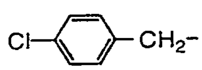
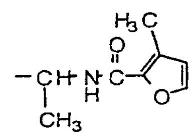
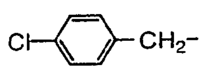
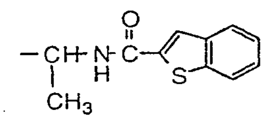
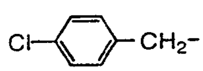
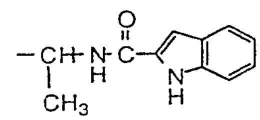
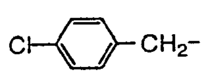
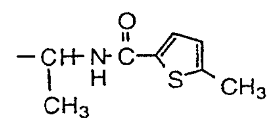
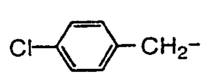
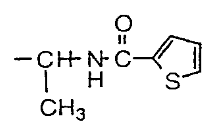
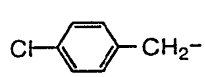
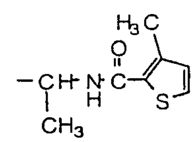
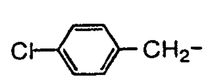
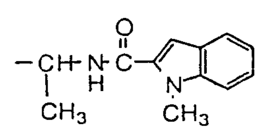
Compd. No.	R^1R^2>$-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
573		2	2	1	-	H	
574		2	2	1	-	H	
575		2	2	1	-	H	
576		2	2	1	-	H	
577		2	2	1	-	H	
578		2	2	1	-	H	
579		2	2	1	-	H	
580		2	2	1	-	H	
581		2	2	1	-	H	
582		2	2	1	-	H	
583		2	2	1	-	H	

Table 1.54

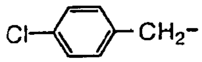
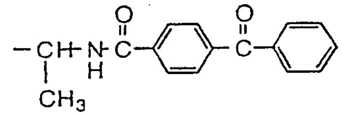
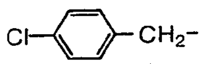
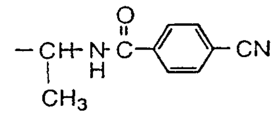
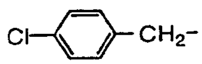
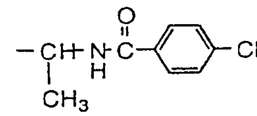
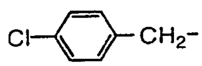
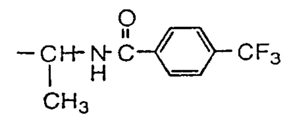
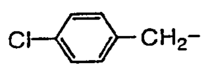
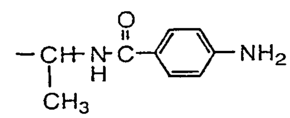
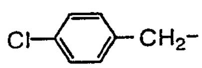
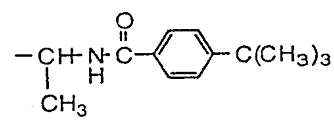
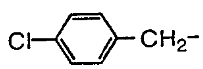
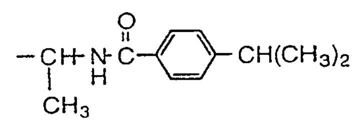
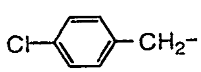
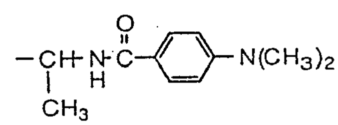
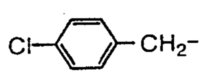
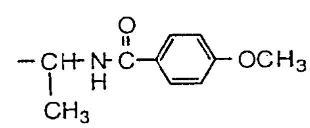
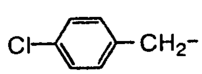
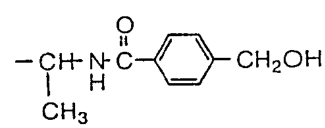
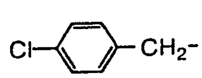
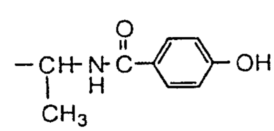
Compd. No.	$R^1R^2>$-$(CH_2)_j$-	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
584		2	2	1	-	H	
585		2	2	1	-	H	
586		2	2	1	-	H	
587		2	2	1	-	H	
588		2	2	1	-	H	
589		2	2	1	-	H	
590		2	2	1	-	H	
591		2	2	1	-	H	
592		2	2	1	-	H	
593		2	2	1	-	H	
594		2	2	1	-	H	

Table 1.55

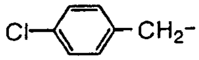
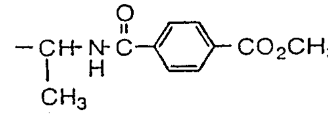
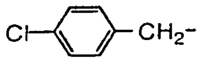
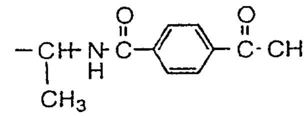
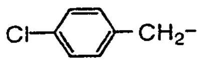
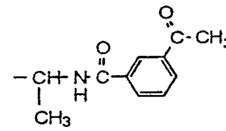
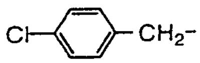
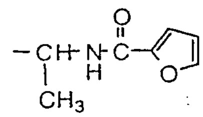
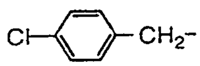
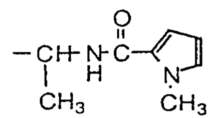
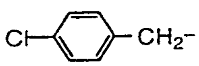
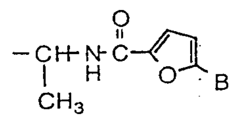
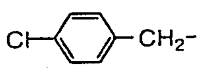
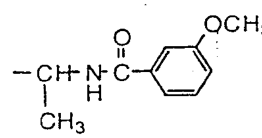
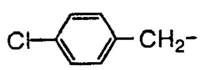
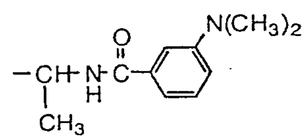
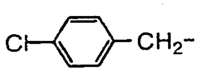
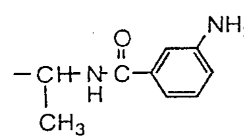
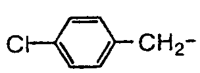
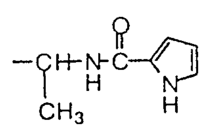
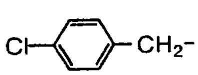
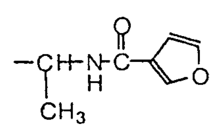
Compd. No.	$R^1(R^2)$>-$(CH_2)_j$-	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
595		2	2	1	-	H	
596		2	2	1	-	H	
597		2	2	1	-	H	
598		2	2	1	-	H	
599		2	2	1	-	H	
600		2	2	1	-	H	
601		2	2	1	-	H	
602		2	2	1	-	H	
603		2	2	1	-	H	
604		2	2	1	-	H	
605		2	2	1	-	H	

Table 1.56

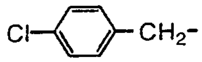
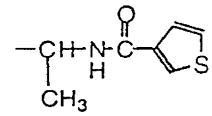
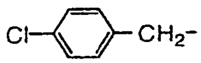
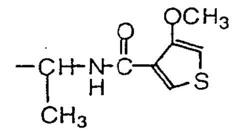
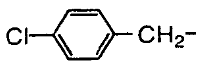
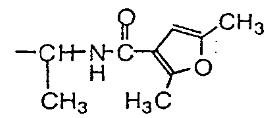
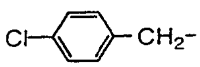
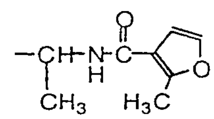
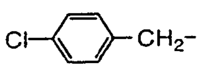
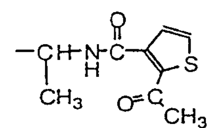
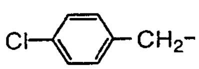
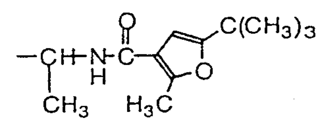
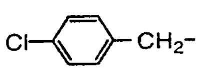
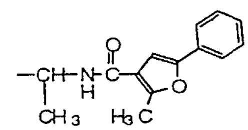
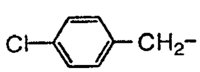
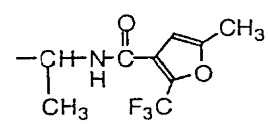
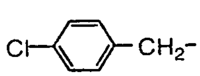
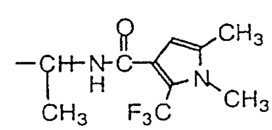
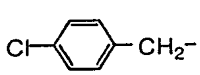
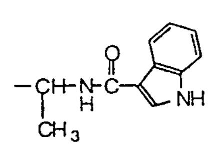
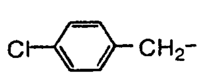
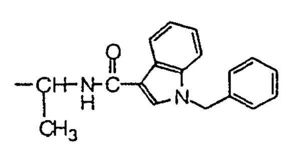
Compd. No.	R^1R^2>—$(CH_2)_j$—	k	m	n	chirality	R^3	—$(CH_2)_p$—$C(R^4)(R^5)$—$(CH_2)_q$—G—R^6
606		2	2	1	-	H	
607		2	2	1	-	H	
608		2	2	1	-	H	
609		2	2	1	-	H	
610		2	2	1	-	H	
611		2	2	1	-	H	
612		2	2	1	-	H	
613		2	2	1	-	H	
614		2	2	1	-	H	
615		2	2	1	-	H	
616		2	2	1	-	H	

Table 1.57

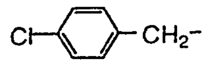
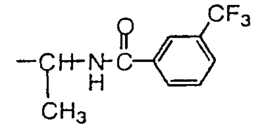
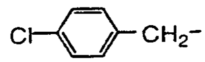
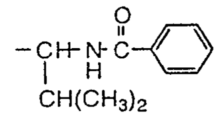
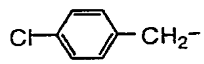
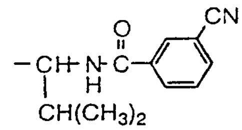
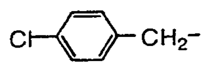
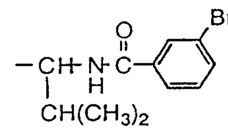
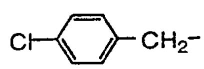
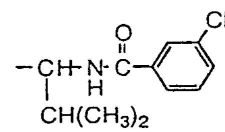
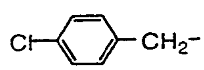
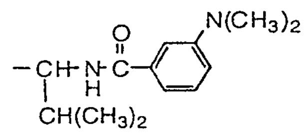
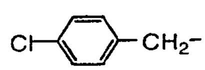
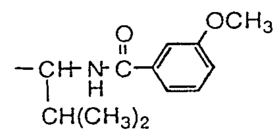
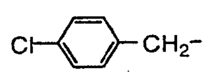
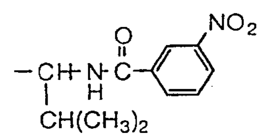
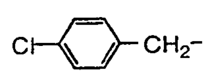
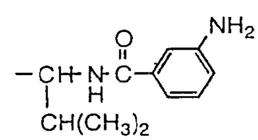
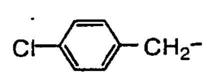
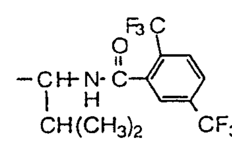
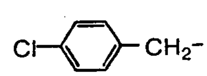
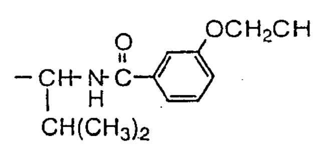
Compd. No.	R^1R^2>-$(CH_2)_j$-	k	m	n	chirality	R^3	-$(CH_2)_p$-$C(R^4)(R^5)$-$(CH_2)_q$-G-R^6
617		2	2	1	-	H	
618		2	2	1	-	H	
619		2	2	1	-	H	
620		2	2	1	-	H	
621		2	2	1	-	H	
622		2	2	1	-	H	
623		2	2	1	-	H	
624		2	2	1	-	H	
625		2	2	1	-	H	
626		2	2	1	-	H	
627		2	2	1	-	H	

Table 1.58

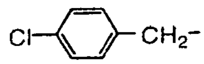
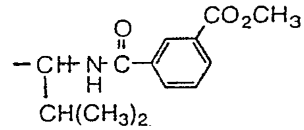
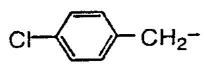
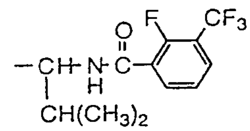
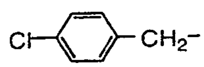
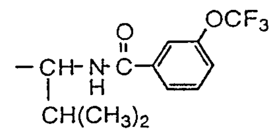
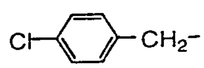
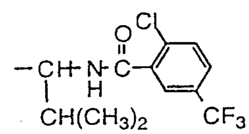
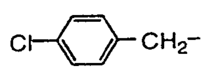
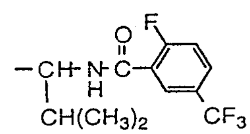
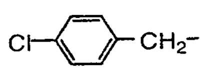
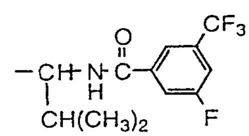
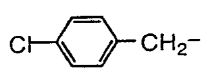
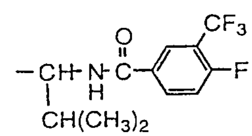
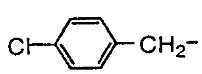
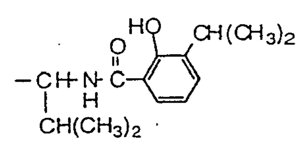
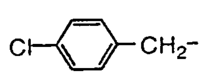
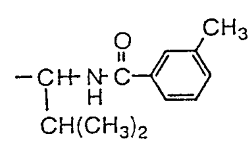
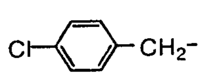
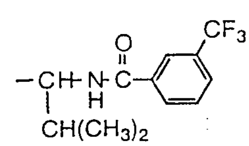
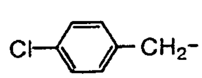
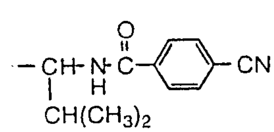
Compd. No.	R^1, R^2 $>$ $-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
628		2	2	1	-	H	
629		2	2	1	-	H	
630		2	2	1	-	H	
631		2	2	1	-	H	
632		2	2	1	-	H	
633		2	2	1	-	H	
634		2	2	1	-	H	
635		2	2	1	-	H	
636		2	2	1	-	H	
637		2	2	1	-	H	
638		2	2	1	-	H	

Table 1.59

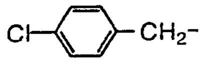
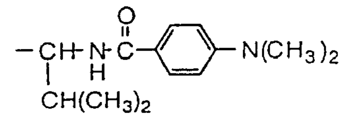
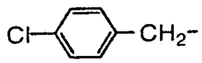
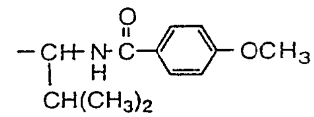
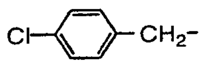
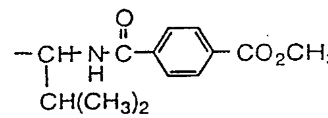
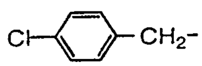
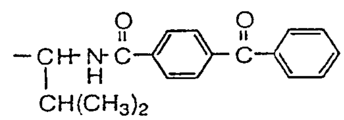
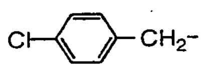
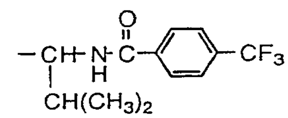
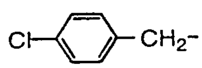
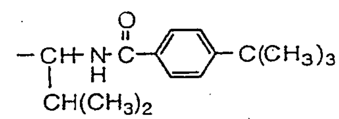
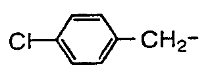
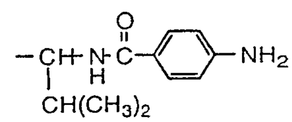
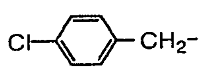
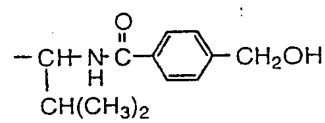
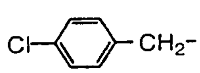
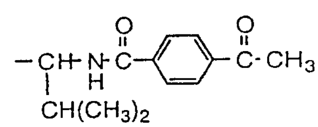
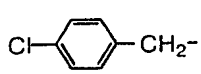
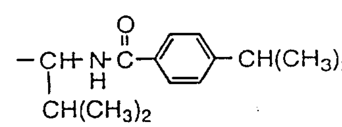
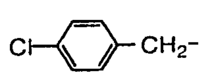
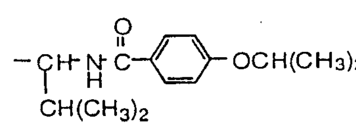
Compd. No.	$\begin{matrix}R^1\\R^2\end{matrix}\!\!>\!\!-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-\overset{R^4}{\underset{R^5}{C}}-(CH_2)_q-G-R^6$
639		2	2	1	-	H	
640		2	2	1	-	H	
641		2	2	1	-	H	
642		2	2	1	-	H	
643		2	2	1	-	H	
644		2	2	1	-	H	
645		2	2	1	-	H	
646		2	2	1	-	H	
647		2	2	1	-	H	
648		2	2	1	-	H	
649		2	2	1	-	H	

Table 1.60

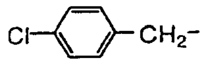
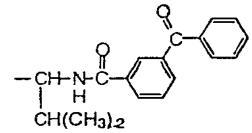
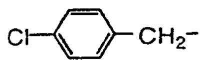
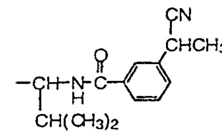
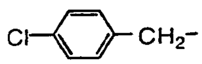
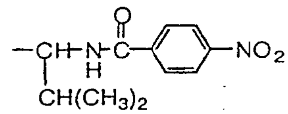
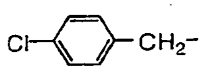
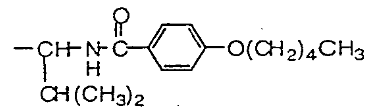
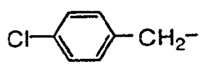
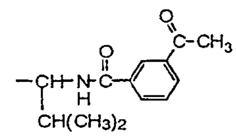
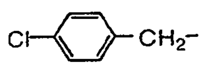
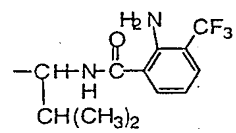
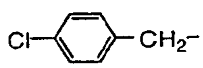
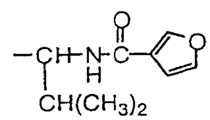
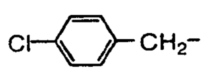
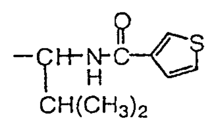
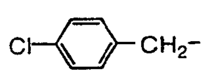
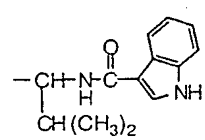
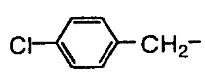
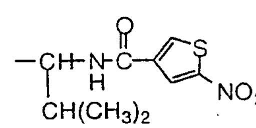
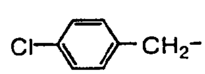
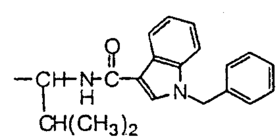
Compd. No.	$R^1(R^2)\rangle-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
650		2	2	1	-	H	
651		2	2	1	-	H	
652		2	2	1	-	H	
653		2	2	1	-	H	
654		2	2	1	-	H	
655		2	2	1	-	H	
656		2	2	1	-	H	
657		2	2	1	-	H	
658		2	2	1	-	H	
659		2	2	1	-	H	
660		2	2	1	-	H	

Table 1.61

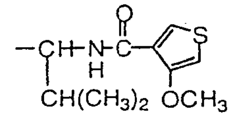
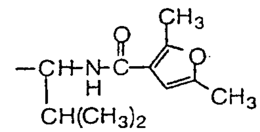
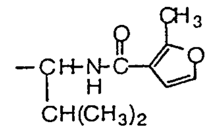
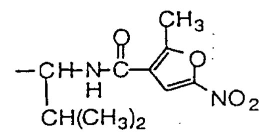
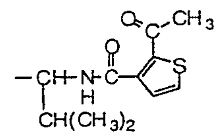
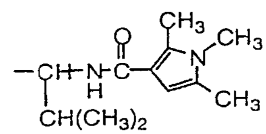
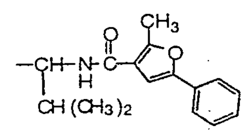
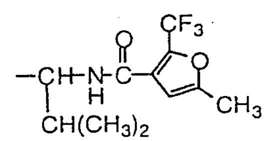
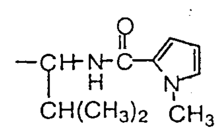
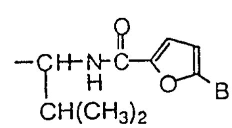
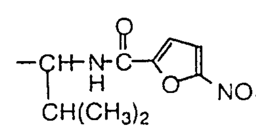
Compd. No.	R^1R^2>-$(CH_2)_j$-	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
661	Cl-C6H4-CH2-	2	2	1	-	H	
662	Cl-C6H4-CH2-	2	2	1	-	H	
663	Cl-C6H4-CH2-	2	2	1	-	H	
664	Cl-C6H4-CH2-	2	2	1	-	H	
665	Cl-C6H4-CH2-	2	2	1	-	H	
666	Cl-C6H4-CH2-	2	2	1	-	H	
667	Cl-C6H4-CH2-	2	2	1	-	H	
668	Cl-C6H4-CH2-	2	2	1	-	H	
669	Cl-C6H4-CH2-	2	2	1	-	H	
670	Cl-C6H4-CH2-	2	2	1	-	H	
671	Cl-C6H4-CH2-	2	2	1	-	H	

Table 1.62

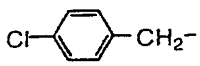
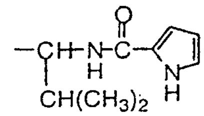
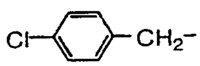
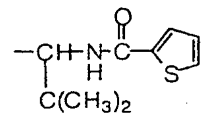
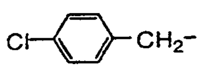
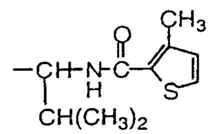
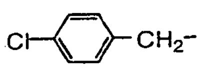
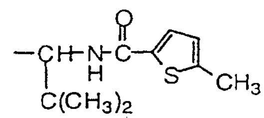
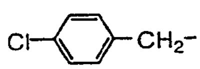
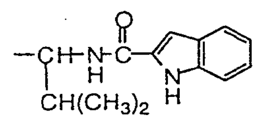
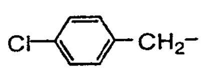
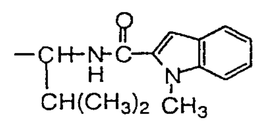
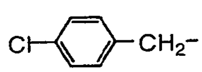
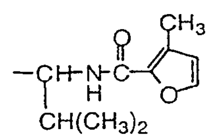
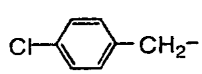
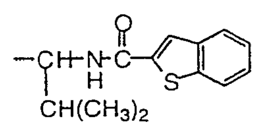
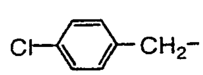
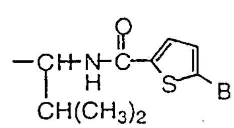
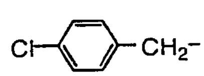
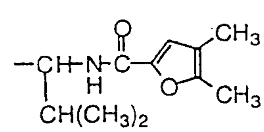
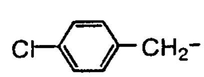
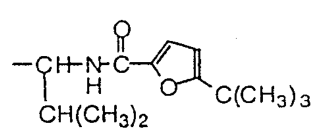
Compd. No.	$R^1R^2>$–$(CH_2)_j$–	k	m	n	chirality	R^3	–$(CH_2)_p$–$C(R^4)(R^5)$–$(CH_2)_q$–G–R^6
672		2	2	1	-	H	
673		2	2	1	-	H	
674		2	2	1	-	H	
675		2	2	1	-	H	
676		2	2	1	-	H	
677		2	2	1	-	H	
678		2	2	1	-	H	
679		2	2	1	-	H	
680		2	2	1	-	H	
681		2	2	1	-	H	
682		2	2	1	-	H	

Table 1.63

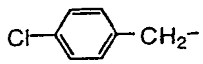
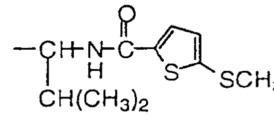
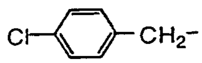
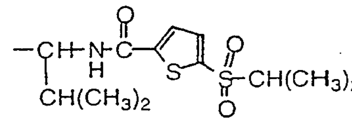
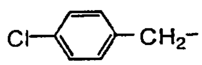
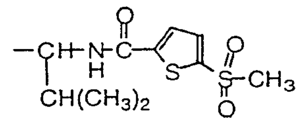
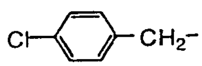
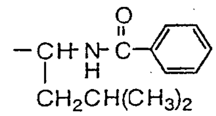
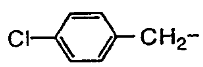
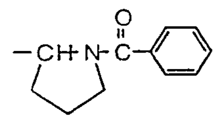
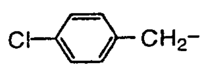
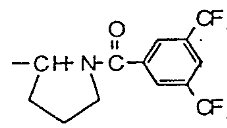
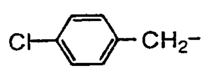
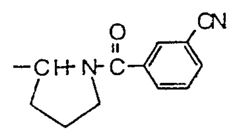
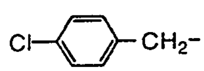
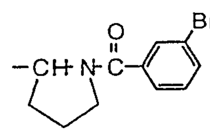
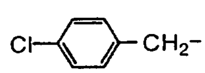
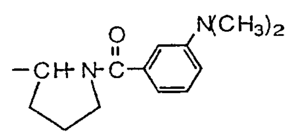
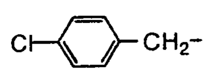
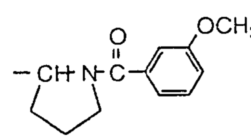
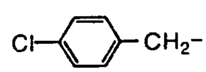
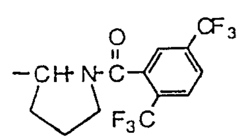
Compd. No.	$R^1R^2>-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
683		2	2	1	-	H	
684		2	2	1	-	H	
685		2	2	1	-	H	
686		2	2	1	-	H	
687		2	2	1	-	H	
688		2	2	1	-	H	
689		2	2	1	-	H	
690		2	2	1	-	H	
691		2	2	1	-	H	
692		2	2	1	-	H	
693		2	2	1	-	H	

Table 1.64

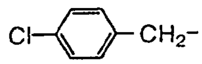
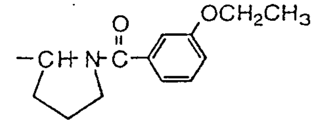
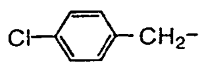
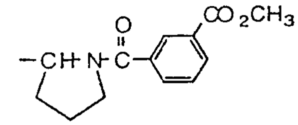
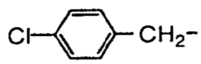
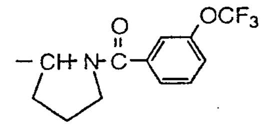
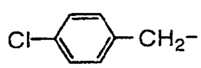
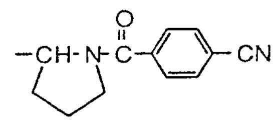
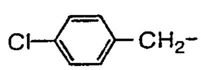
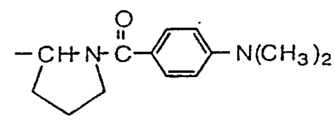
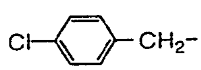
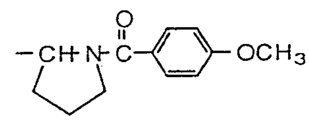
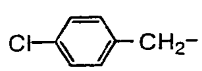
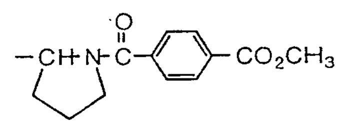
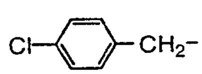
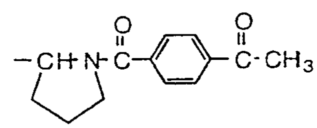
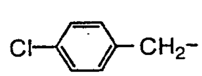
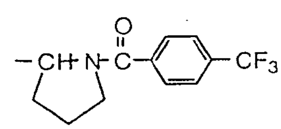
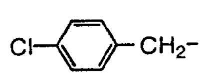
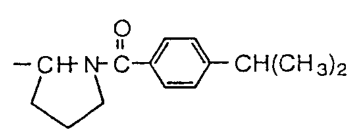
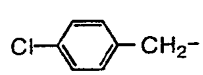
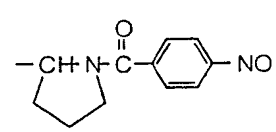
Compd. No.	$R^1R^2>$—$(CH_2)_j$—	k	m	n	chirality	R^3	—$(CH_2)_p$—$C(R^4)(R^5)$—$(CH_2)_q$—G—R^6
694		2	2	1	-	H	
695		2	2	1	-	H	
696		2	2	1	-	H	
697		2	2	1	-	H	
698		2	2	1	-	H	
699		2	2	1	-	H	
700		2	2	1	-	H	
701		2	2	1	-	H	
702		2	2	1	-	H	
703		2	2	1	-	H	
704		2	2	1	-	H	

Table 1.65

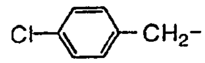
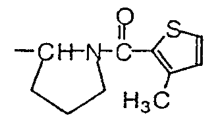
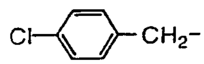
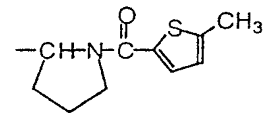
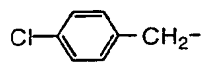
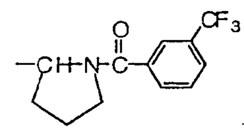
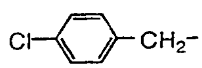
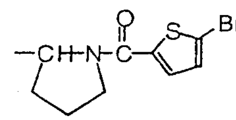
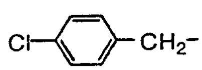
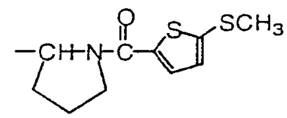
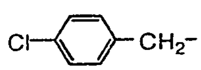
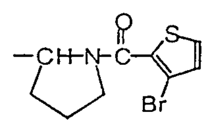
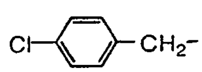
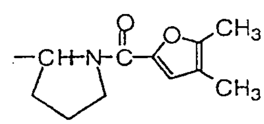
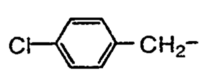
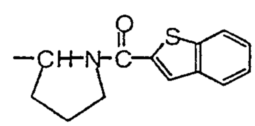
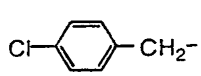
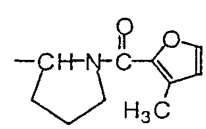
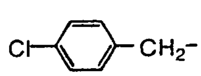
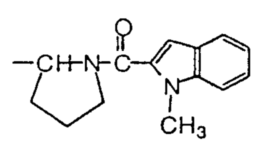
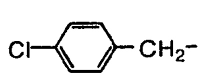
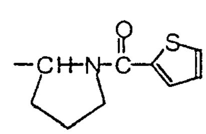
Compd. No.	R^1R^2>-$(CH_2)_j$–	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
705		2	2	1	-	H	
706		2	2	1	-	H	
707		2	2	1	-	H	
708		2	2	1	-	H	
709		2	2	1	-	H	
710		2	2	1	-	H	
711		2	2	1	-	H	
712		2	2	1	-	H	
713		2	2	1	-	H	
714		2	2	1	-	H	
715		2	2	1	-	H	

Table 1.66

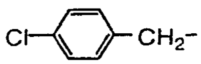
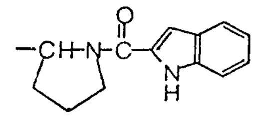
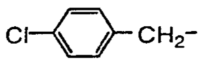
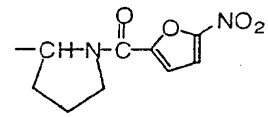
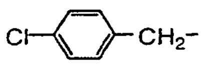
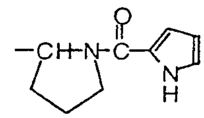
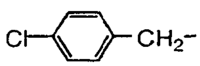
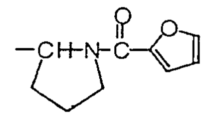
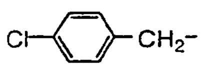
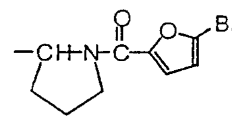
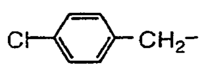
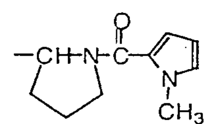
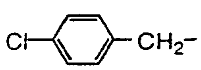
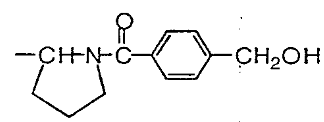
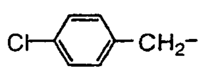
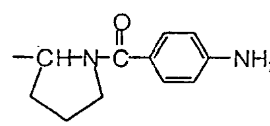
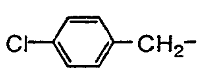
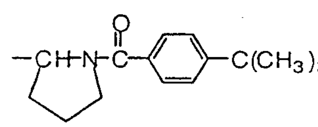
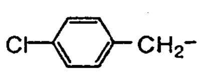
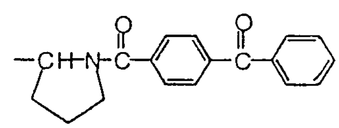
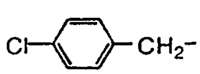
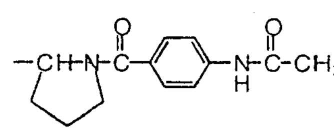
Compd. No.	$R^1R^2>(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
716		2	2	1	-	H	
717		2	2	1	-	H	
718		2	2	1	-	H	
719		2	2	1	-	H	
720		2	2	1	-	H	
721		2	2	1	-	H	
722		2	2	1	-	H	
723		2	2	1	-	H	
724		2	2	1	-	H	
725		2	2	1	-	H	
726		2	2	1	-	H	

Table 1.67

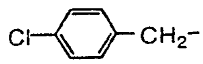
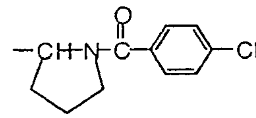
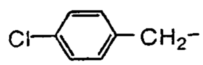
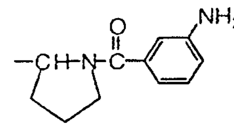
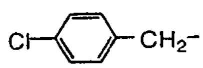
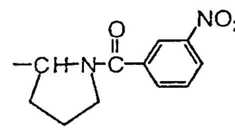
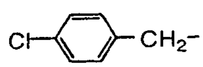
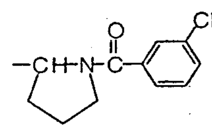
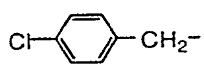
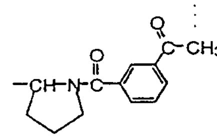
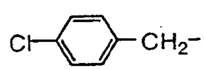
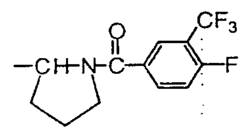
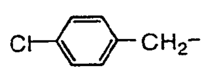
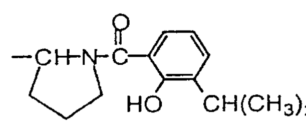
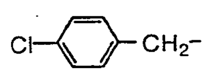
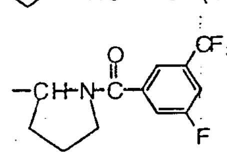
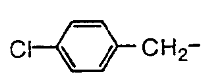
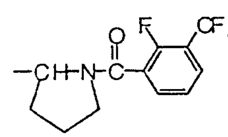
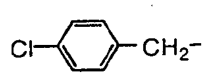
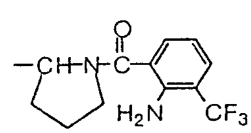
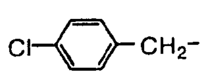
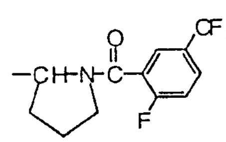
Compd. No.	$R^1R^2>-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
727		2	2	1	-	H	
728		2	2	1	-	H	
729		2	2	1	-	H	
730		2	2	1	-	H	
731		2	2	1	-	H	
732		2	2	1	-	H	
733		2	2	1	-	H	
734		2	2	1	-	H	
735		2	2	1	-	H	
736		2	2	1	-	H	
737		2	2	1	-	H	

Table 1.68

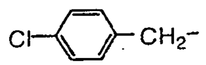
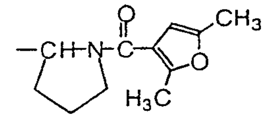
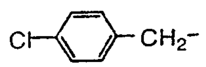
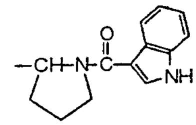
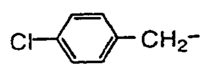
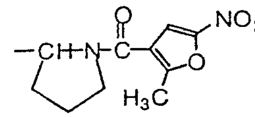
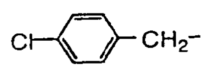
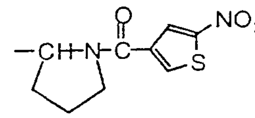
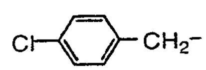
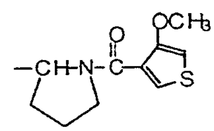
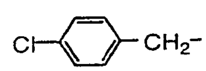
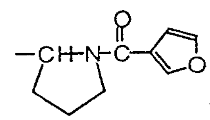
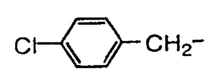
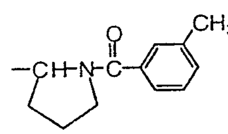
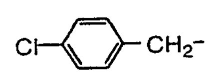
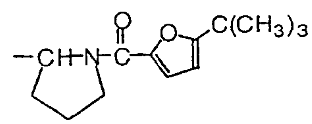
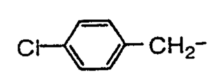
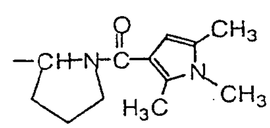
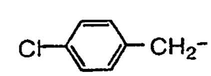
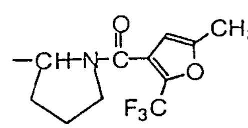
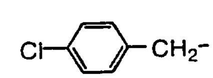
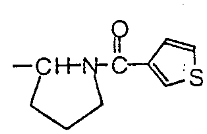
Compd. No.	$R^1R^2>$-$(CH_2)_j$-	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
738		2	2	1	-	H	
739		2	2	1	-	H	
740		2	2	1	-	H	
741		2	2	1	-	H	
742		2	2	1	-	H	
743		2	2	1	-	H	
744		2	2	1	-	H	
745		2	2	1	-	H	
746		2	2	1	-	H	
747		2	2	1	-	H	
748		2	2	1	-	H	

Table 1.69

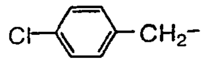
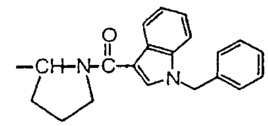
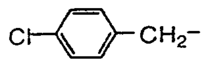
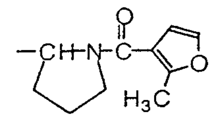
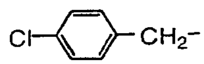
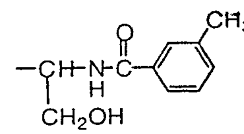
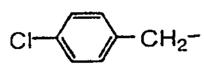
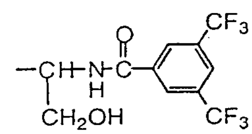
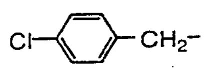
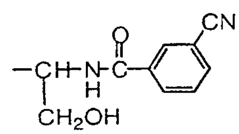
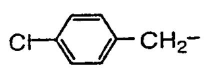
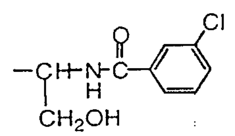
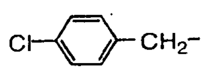
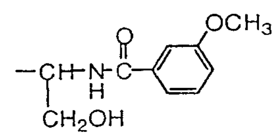
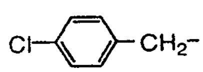
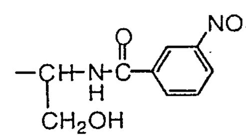
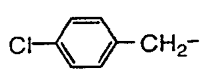
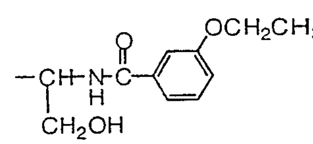
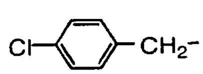
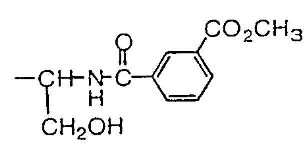
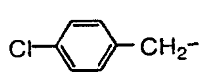
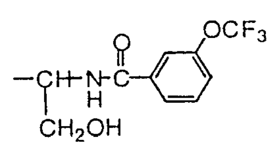
Compd. No.	R^1, R^2 $>$—$(CH_2)_j$—	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
749		2	2	1	-	H	
750		2	2	1	-	H	
751		2	2	1	-	H	
752		2	2	1	-	H	
753		2	2	1	-	H	
754		2	2	1	-	H	
755		2	2	1	-	H	
756		2	2	1	-	H	
757		2	2	1	-	H	
758		2	2	1	-	H	
759		2	2	1	-	H	

Table 1.70

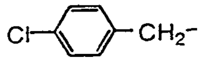
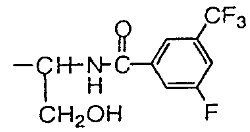
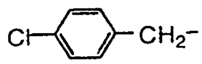
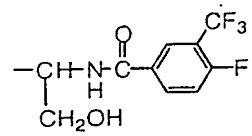
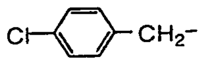
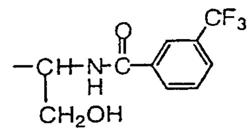
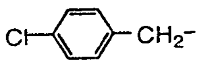
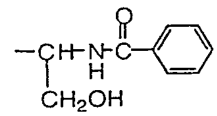
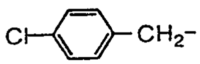
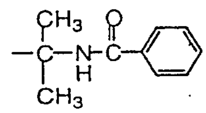
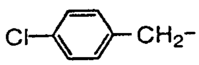
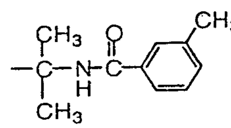
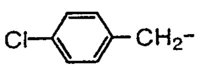
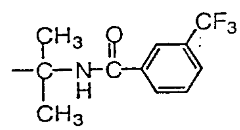
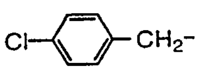
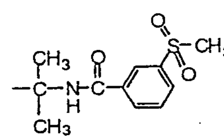
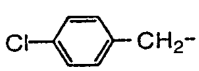
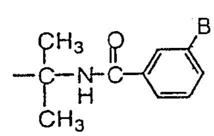
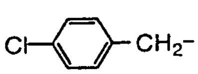
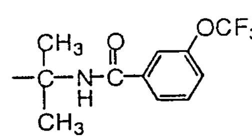
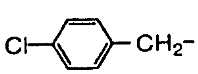
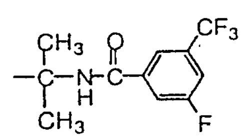
Compd. No.	$R^1R^2>-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
760		2	2	1	-	H	
761		2	2	1	-	H	
762		2	2	1	-	H	
763		2	2	1	-	H	
764		2	2	1	-	H	
765		2	2	1	-	H	
766		2	2	1	-	H	
767		2	2	1	-	H	
768		2	2	1	-	H	
769		2	2	1	-	H	
770		2	2	1	-	H	

Table 1.71

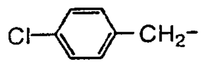
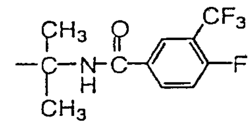
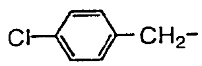
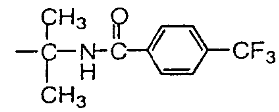
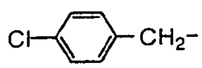
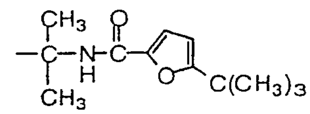
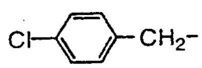
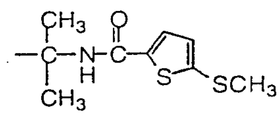
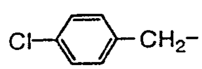
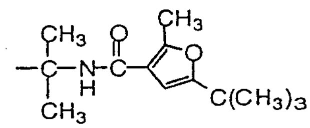
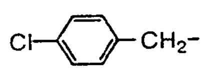
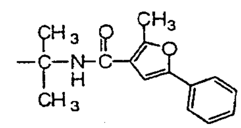
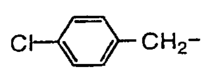
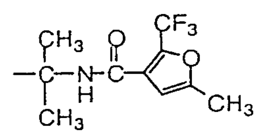
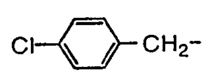
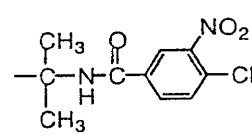
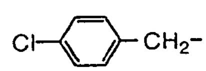
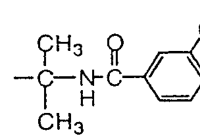
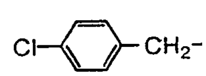
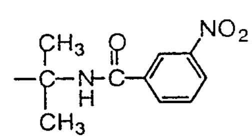
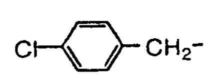
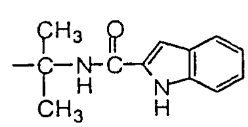
Compd. No.	$R^1R^2{>}(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
771		2	2	1	-	H	
772		2	2	1	-	H	
773		2	2	1	-	H	
774		2	2	1	-	H	
775		2	2	1	-	H	
776		2	2	1	-	H	
777		2	2	1	-	H	
778		2	2	1	-	H	
779		2	2	1	-	H	
780		2	2	1	-	H	
781		2	2	1	-	H	

Table 1.72

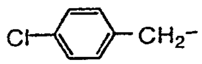
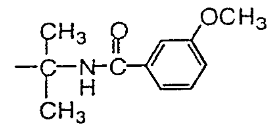
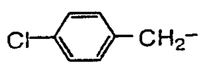
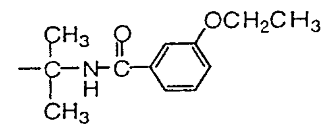
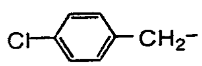
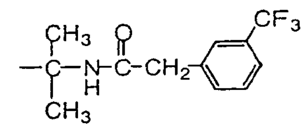
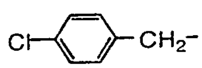
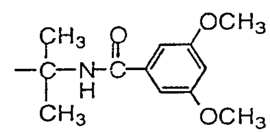
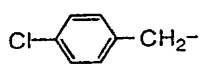
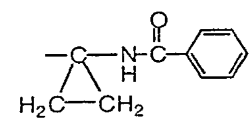
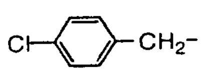
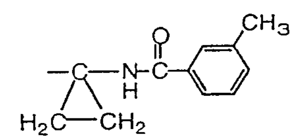
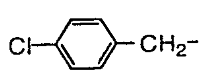
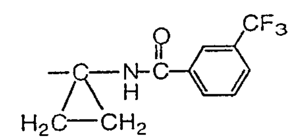
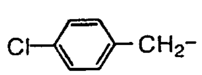
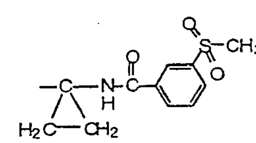
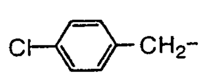
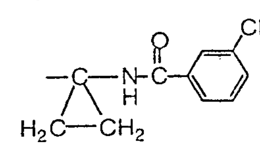
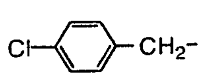
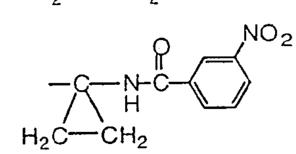
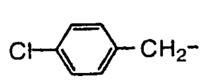
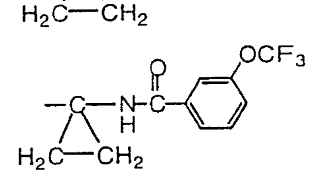
Compd. No.	R^1R^2>-$(CH_2)_j$–	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
782		2	2	1	-	H	
783		2	2	1	-	H	
784		2	2	1	-	H	
785		2	2	1	-	H	
786		2	2	1	-	H	
787		2	2	1	-	H	
788		2	2	1	-	H	
789		2	2	1	-	H	
790		2	2	1	-	H	
791		2	2	1	-	H	
792		2	2	1	-	H	

Table 1.73

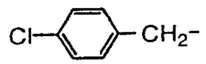
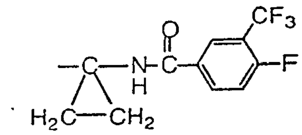
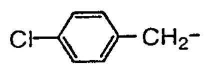
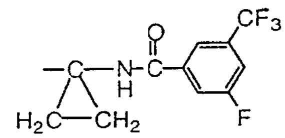
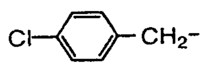
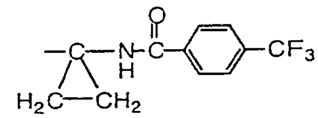
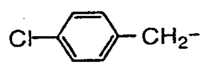
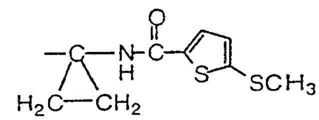
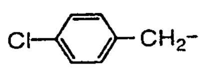
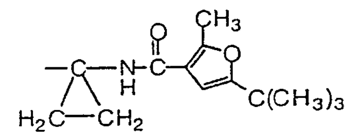
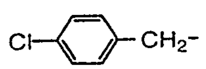
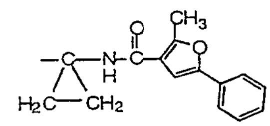
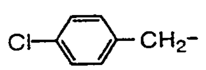
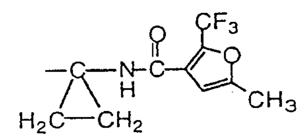
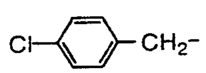
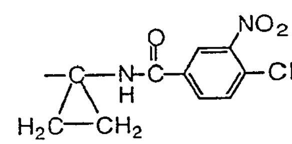
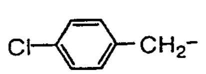
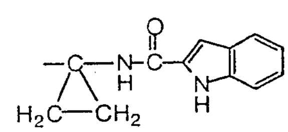
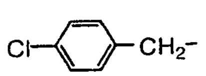
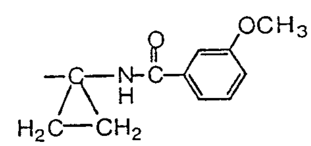
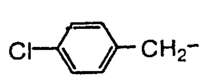
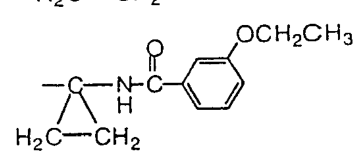
Compd. No.	$R^1R^2>(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
793		2	2	1	-	H	
794		2	2	1	-	H	
795		2	2	1	-	H	
796		2	2	1	-	H	
797		2	2	1	-	H	
798		2	2	1	-	H	
799		2	2	1	-	H	
800		2	2	1	-	H	
801		2	2	1	-	H	
802		2	2	1	-	H	
803		2	2	1	-	H	

Table 1.74

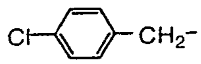
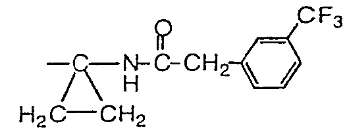
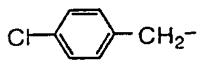
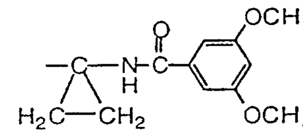
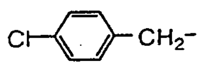
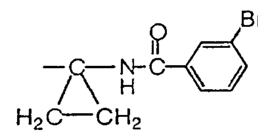
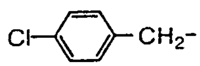
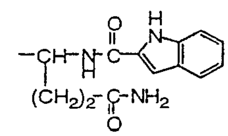
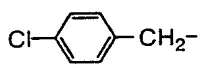
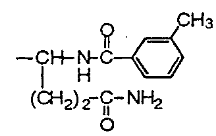
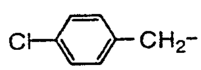
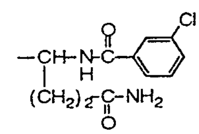
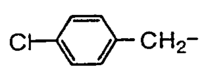
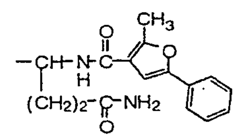
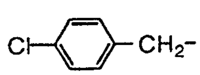
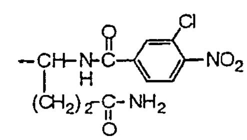
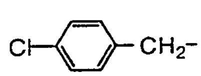
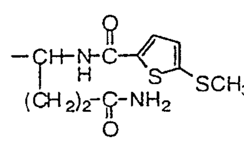
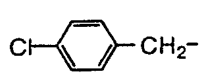
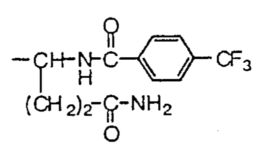
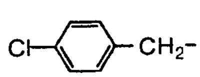
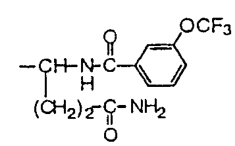
Compd. No.	R^1R^2>$(CH_2)_j$–	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
804		2	2	1	-	H	
805		2	2	1	-	H	
806		2	2	1	-	H	
807		2	2	1	-	H	
808		2	2	1	-	H	
809		2	2	1	-	H	
810		2	2	1	-	H	
811		2	2	1	-	H	
812		2	2	1	-	H	
813		2	2	1	-	H	
814		2	2	1	-	H	

Table 1.75

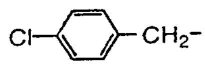
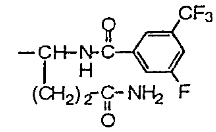
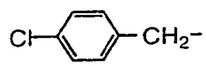
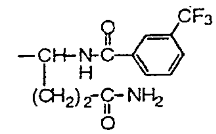
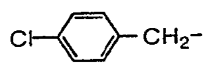
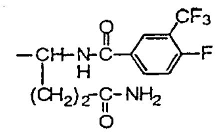
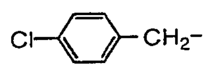
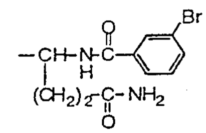
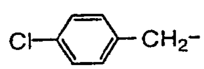
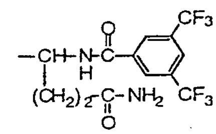
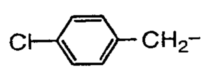
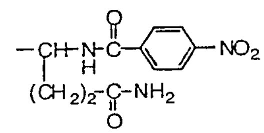
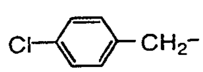
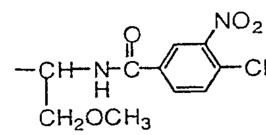
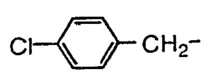
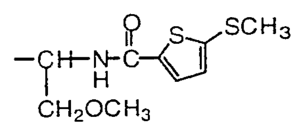
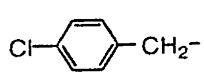
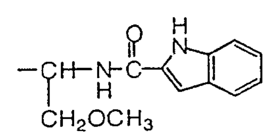
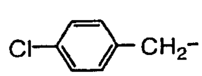
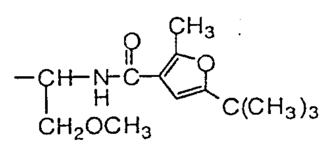
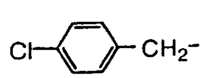
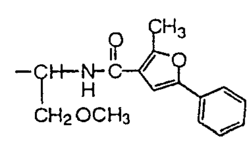
Compd. No.	$R^1R^2>$—$(CH_2)_j$—	k	m	n	chirality	R^3	—$(CH_2)_p$—$C(R^4)(R^5)$—$(CH_2)_q$—G—R^6
815		2	2	1	-	H	
816		2	2	1	-	H	
817		2	2	1	-	H	
818		2	2	1	-	H	
819		2	2	1	-	H	
820		2	2	1	-	H	
821		2	2	1	-	H	
822		2	2	1	-	H	
823		2	2	1	-	H	
824		2	2	1	-	H	
825		2	2	1	-	H	

Table 1.76

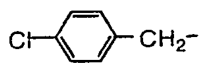
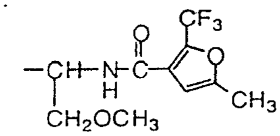
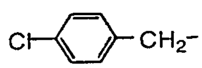
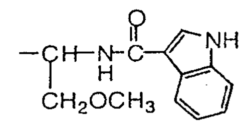
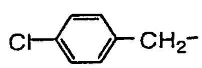
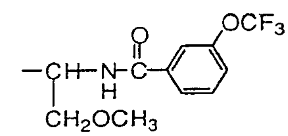
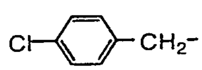
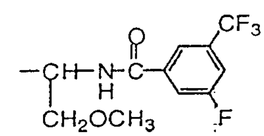
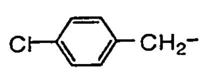
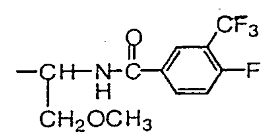
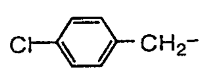
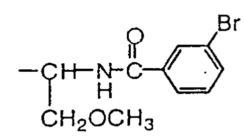
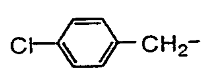
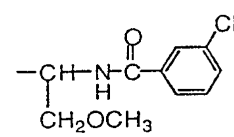
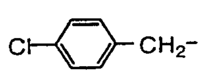
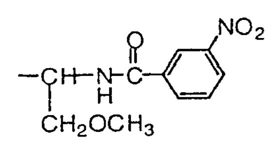
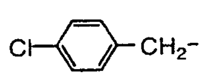
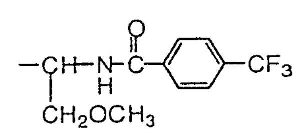
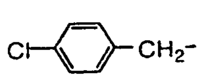
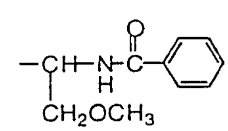
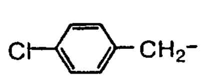
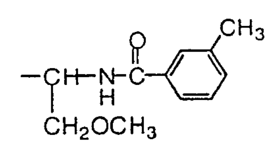
Compd. No.	$R^1R^2>-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
826		2	2	1	-	H	
827		2	2	1	-	H	
828		2	2	1	-	H	
829		2	2	1	-	H	
830		2	2	1	-	H	
831		2	2	1	-	H	
832		2	2	1	-	H	
833		2	2	1	-	H	
834		2	2	1	-	H	
835		2	2	1	-	H	
836		2	2	1	-	H	

Table 1.77

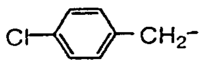
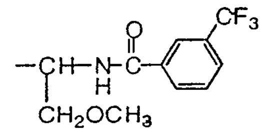
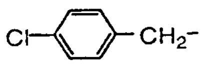
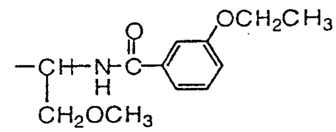
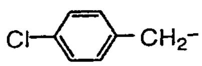
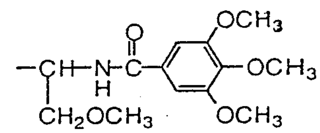
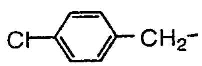
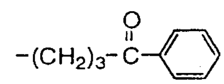
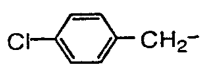
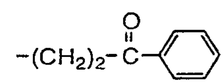
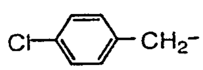
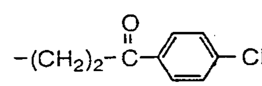
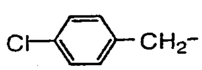
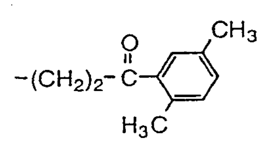
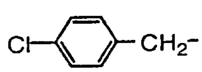
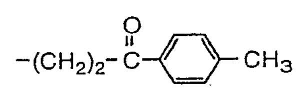
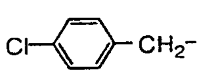
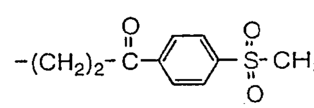
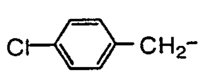
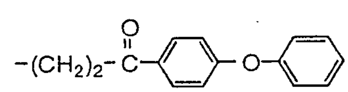
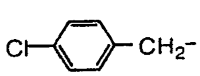
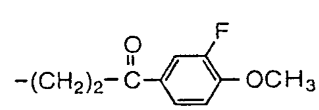
Compd. No.	$R^1R^2{>}(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
837		2	2	1	-	H	
838		2	2	1	-	H	
839		2	2	1	-	H	
840		2	2	1	-	H	
841		2	2	1	-	H	
842		2	2	1	-	H	
843		2	2	1	-	H	
844		2	2	1	-	H	
845		2	2	1	-	H	
846		2	2	1	-	H	
847		2	2	1	-	H	

Table 1.78

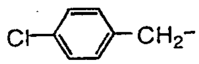
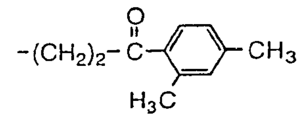
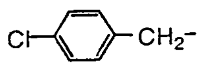
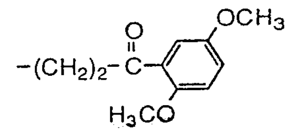
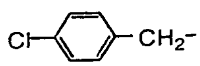
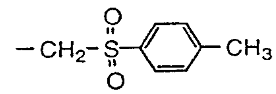
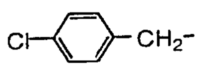
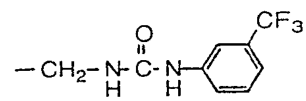
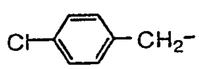
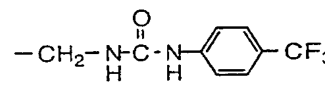
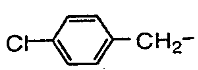
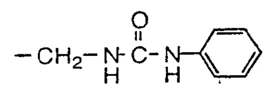
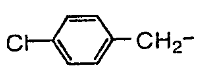
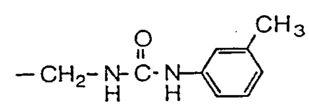
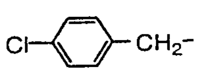
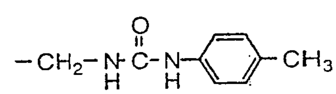
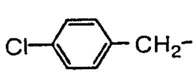
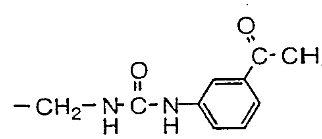
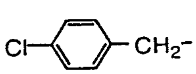
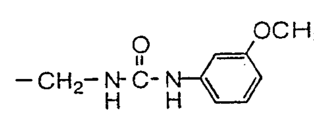
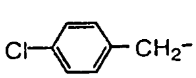
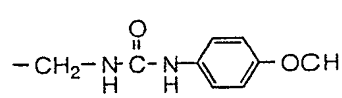
Compd. No.	R^1R^2>-$(CH_2)_j$-	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
848		2	2	1	-	H	
849		2	2	1	-	H	
850		2	2	1	-	H	
851		2	2	1	-	H	
852		2	2	1	-	H	
853		2	2	1	-	H	
854		2	2	1	-	H	
855		2	2	1	-	H	
856		2	2	1	-	H	
857		2	2	1	-	H	
858		2	2	1	-	H	

Table 1.79

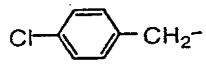
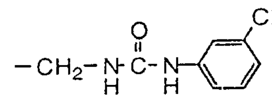
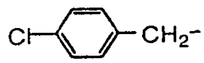
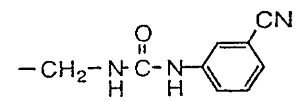
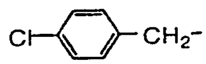
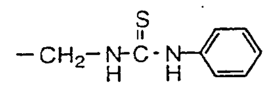
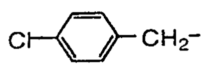
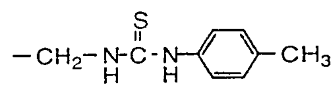
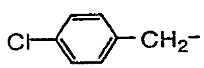
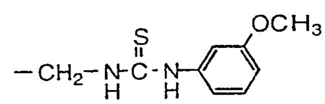
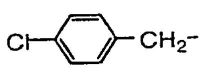
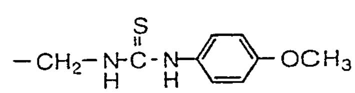
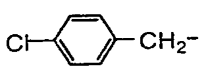
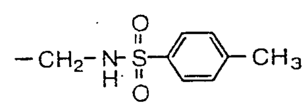
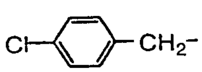
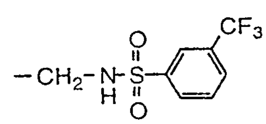
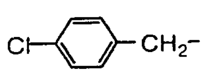
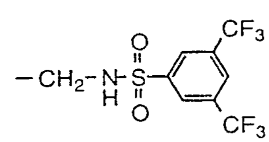
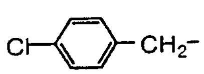
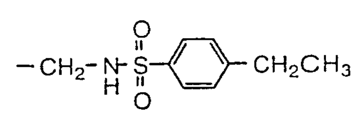
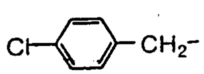
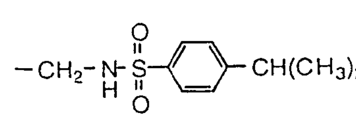
Compd. No.	$R^1R^2C-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
859		2	2	1	-	H	
860		2	2	1	-	H	
861		2	2	1	-	H	
862		2	2	1	-	H	
863		2	2	1	-	H	
864		2	2	1	-	H	
865		2	2	1	-	H	
866		2	2	1	-	H	
867		2	2	1	-	H	
868		2	2	1	-	H	
869		2	2	1	-	H	

Table 1.80

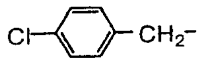
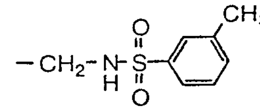
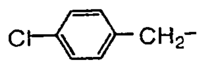
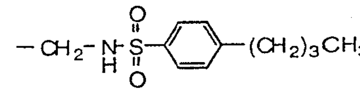
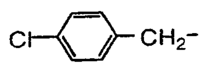
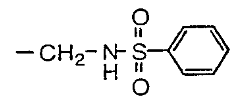
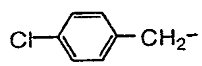
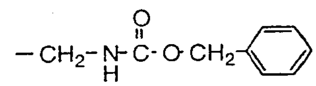
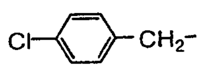
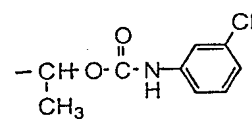
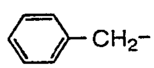
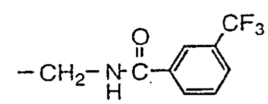
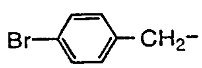
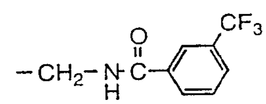
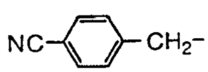
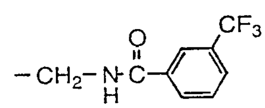
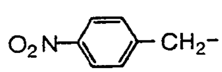
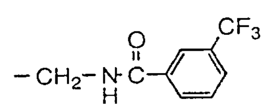
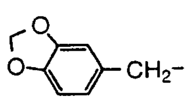
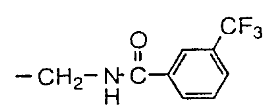
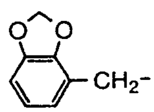
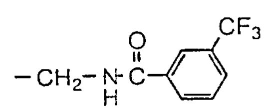
Compd. No.	$R^1R^2 \rangle (CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-\overset{R^4}{\underset{R^5}{C}}-(CH_2)_q-G-R^6$
870		2	2	1	-	H	
871		2	2	1	-	H	
872		2	2	1	-	H	
873		2	2	1	-	H	
874		2	2	1	-	H	
875		2	2	1	-	H	
876		2	2	1	-	H	
877		2	2	1	-	H	
878		2	2	1	-	H	
879		2	2	1	-	H	
880		2	2	1	-	H	

Table 1.81

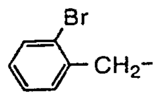
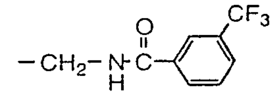
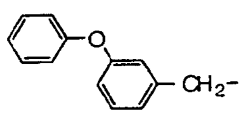
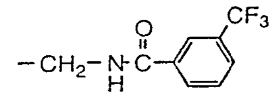
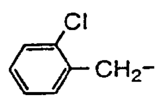
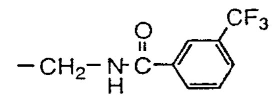
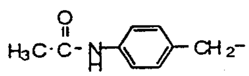
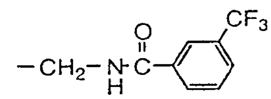
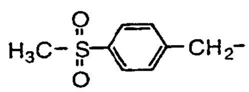
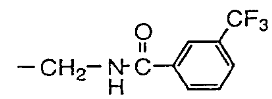
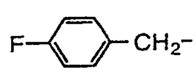
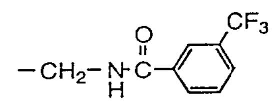
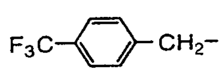
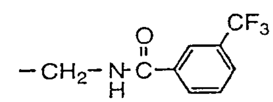
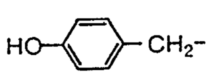
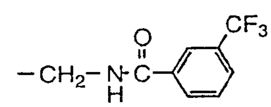
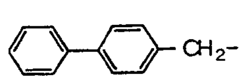
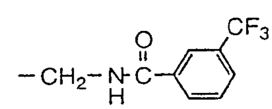
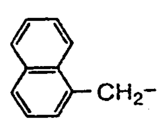
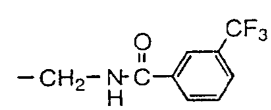
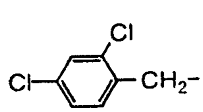
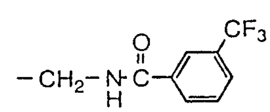
Compd. No.	R^1, R^2 $>$–$(CH_2)_j$–	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
881		2	2	1	-	H	
882		2	2	1	-	H	
883		2	2	1	-	H	
884		2	2	1	-	H	
885		2	2	1	-	H	
886		2	2	1	-	H	
887		2	2	1	-	H	
888		2	2	1	-	H	
889		2	2	1	-	H	
890		2	2	1	-	H	
891		2	2	1	-	H	

Table 1.82

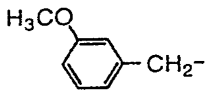
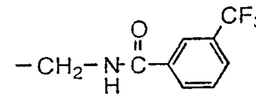
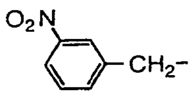
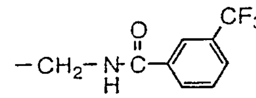
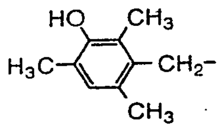
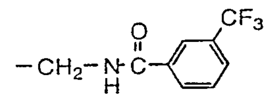
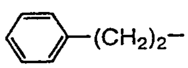
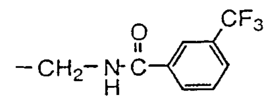
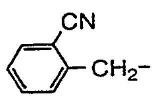
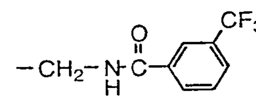
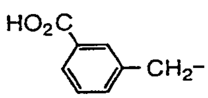
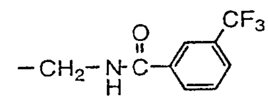
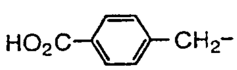
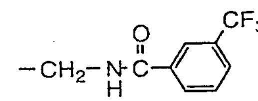
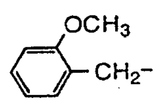
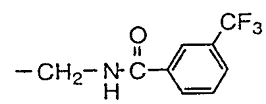
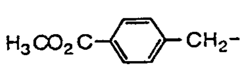
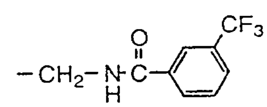
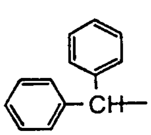
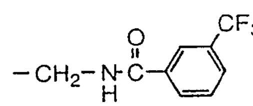
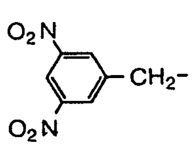
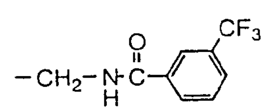
Compd. No.	R^1R^2>-$(CH_2)_j$-	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
892		2	2	1	-	H	
893		2	2	1	-	H	
894		2	2	1	-	H	
895		2	2	1	-	H	
896		2	2	1	-	H	
897		2	2	1	-	H	
898		2	2	1	-	H	
899		2	2	1	-	H	
900		2	2	1	-	H	
901		2	2	1	-	H	
902		2	2	1	-	H	

Table 1.83

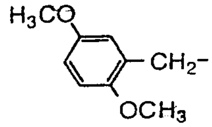
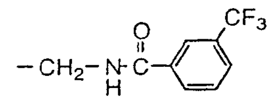
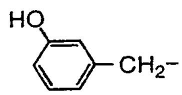
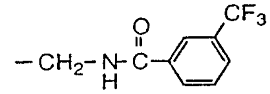
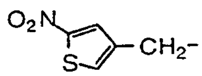
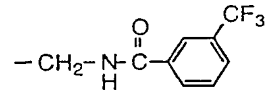
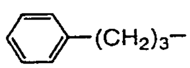
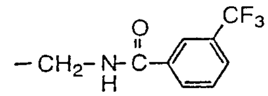
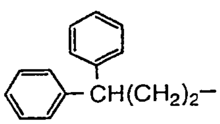
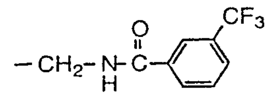
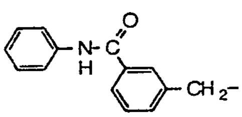
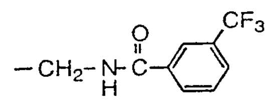
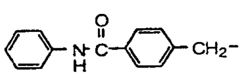
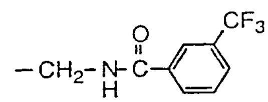
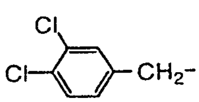
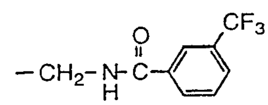
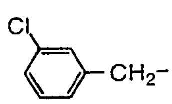
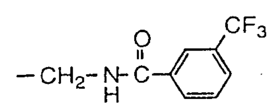
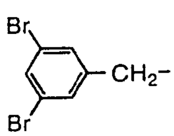
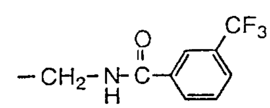
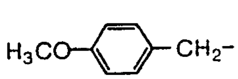
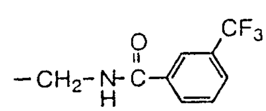
Compd. No.	R^1R^2>$-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
903		2	2	1	-	H	
904		2	2	1	-	H	
905		2	2	1	-	H	
906		2	2	1	-	H	
907		2	2	1	-	H	
908		2	2	1	-	H	
909		2	2	1	-	H	
910		2	2	1	-	H	
911		2	2	1	-	H	
912		2	2	1	-	H	
913		2	2	1	-	H	

Table 1.84

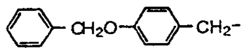
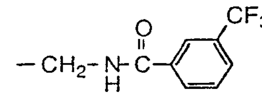
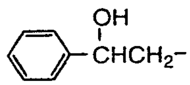
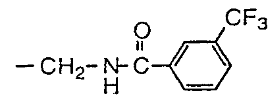
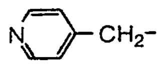
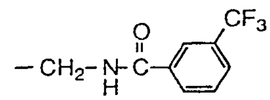
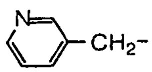
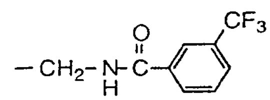
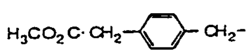
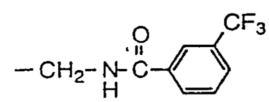
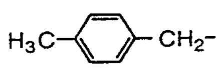
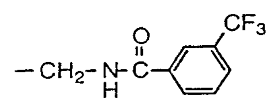
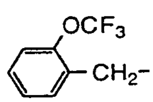
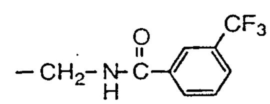
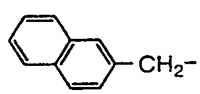
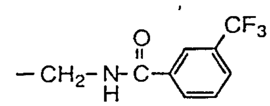
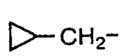
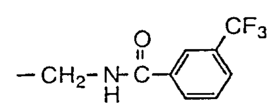
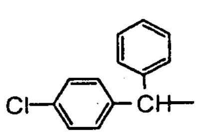
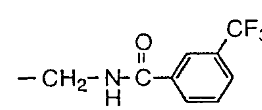
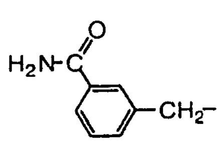
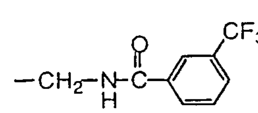
Compd. No.	R^1R^2>$-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
914		2	2	1	-	H	
915		2	2	1	-	H	
916		2	2	1	-	H	
917		2	2	1	-	H	
918		2	2	1	-	H	
919		2	2	1	-	H	
920		2	2	1	-	H	
921		2	2	1	-	H	
922		2	2	1	-	H	
923		2	2	1	-	H	
924		2	2	1	-	H	

Table 1.85

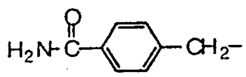
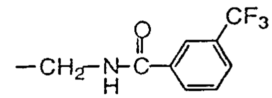
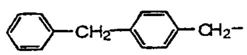
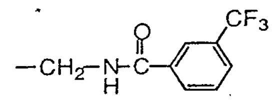
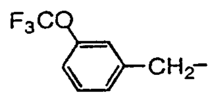
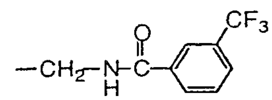
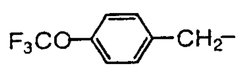
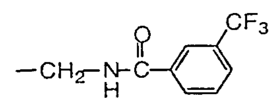
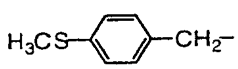
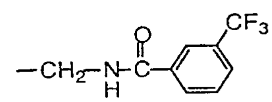
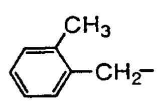
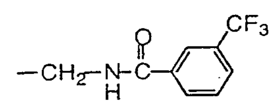
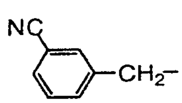
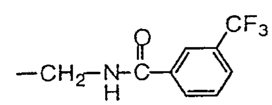
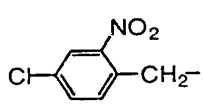
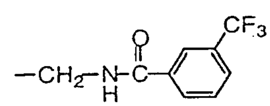
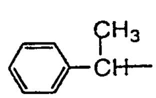
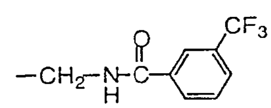
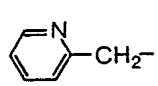
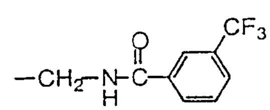
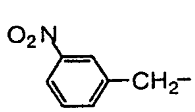
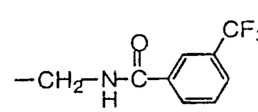
Compd. No.	$R^1R^2{>}{-}(CH_2)_j{-}$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
925		2	2	1	-	H	
926		2	2	1	-	H	
927		2	2	1	-	H	
928		2	2	1	-	H	
929		2	2	1	-	H	
930		2	2	1	-	H	
931		2	2	1	-	H	
932		2	2	1	-	H	
933		2	2	1	-	H	
934		2	2	1	-	H	
935		2	2	1	-	H	

Table 1.86

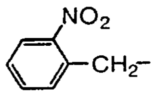
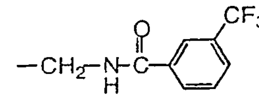
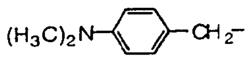
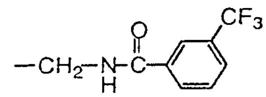
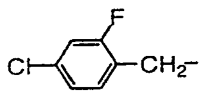
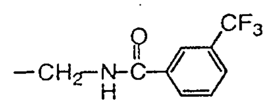
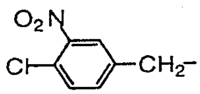
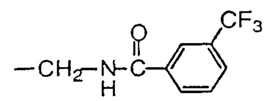
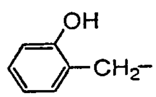
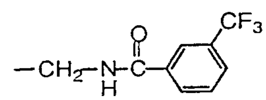
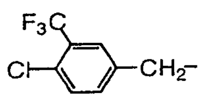
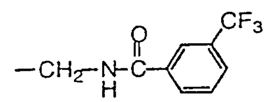
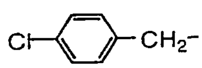
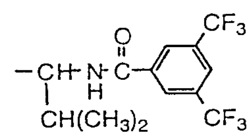
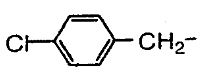
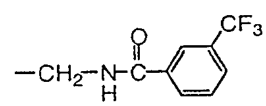
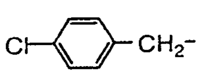
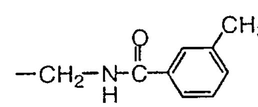
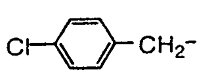
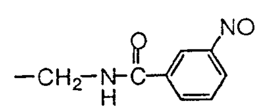
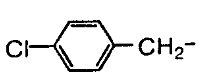
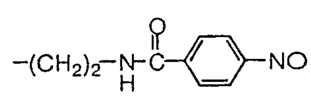
Compd. No.	$R^1R^2\!>\!(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
936		2	2	1	-	H	
937		2	2	1	-	H	
938		2	2	1	-	H	
939		2	2	1	-	H	
940		2	2	1	-	H	
941		2	2	1	-	H	
942		2	2	1	-	H	
943		1	4	0	-	H	
944		1	4	0	-	H	
945		1	4	0	-	H	
946		1	4	0	-	H	

Table 1.87

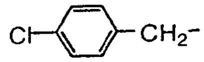
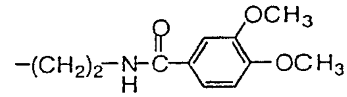
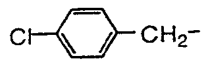
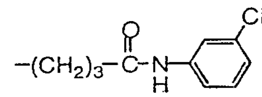
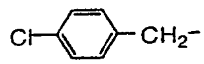
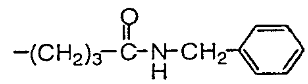
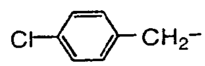
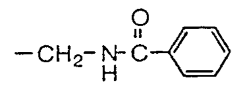
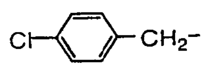
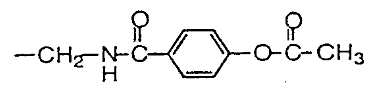
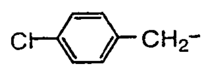
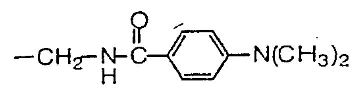
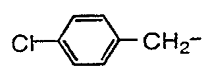
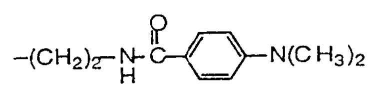
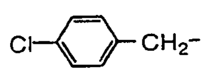
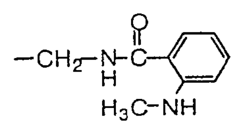
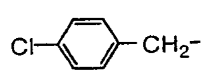
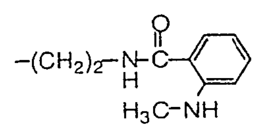
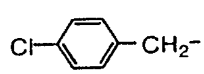
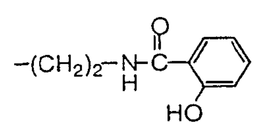
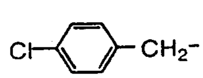
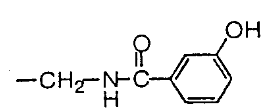
Compd. No.	R^1, R^2 >—$(CH_2)_j$—	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
947		1	4	0	-	H	
948		1	4	0	-	H	
949		1	4	0	-	H	
950		0	4	1	-	H	
951		1	2	0	R	H	
952		1	2	0	R	H	
953		1	2	0	R	H	
954		1	2	0	R	H	
955		1	2	0	R	H	
956		1	2	0	R	H	
957		1	2	0	R	H	

Table 1.88

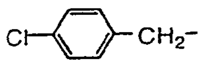
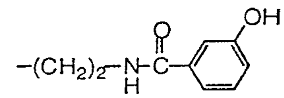
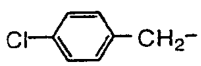
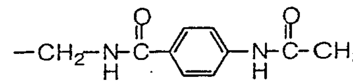
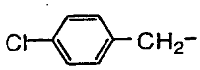
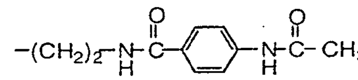
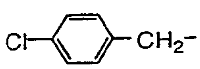
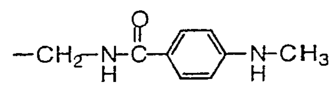
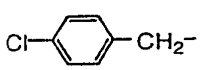
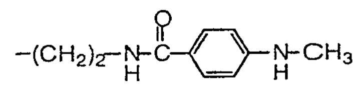
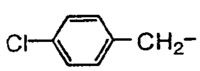
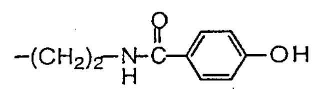
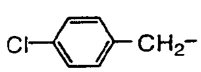
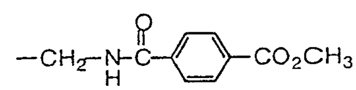
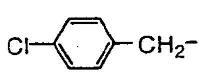
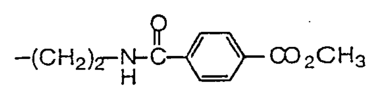
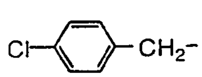
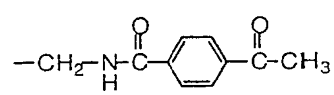
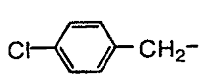
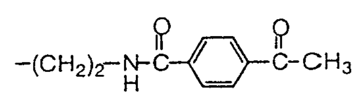
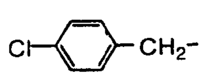
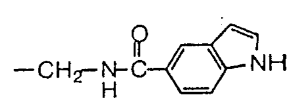
Compd. No.	$R^1R^2>-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
958		1	2	0	R	H	
959		1	2	0	R	H	
960		1	2	0	R	H	
961		1	2	0	R	H	
962		1	2	0	R	H	
963		1	2	0	R	H	
964		1	2	0	R	H	
965		1	2	0	R	H	
966		1	2	0	R	H	
967		1	2	0	R	H	
968		1	2	0	R	H	

Table 1.89

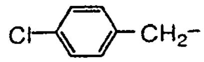
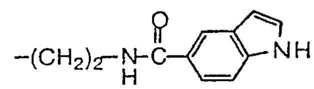
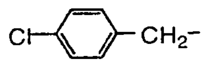
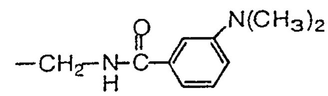
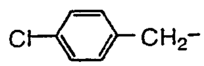
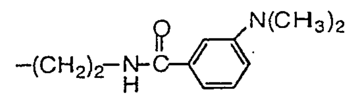
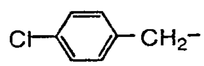
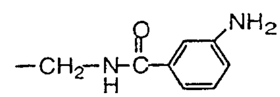
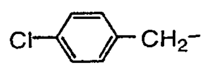
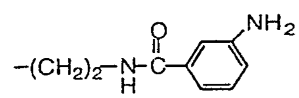
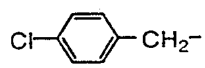
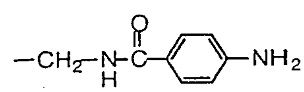
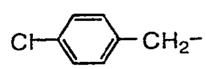
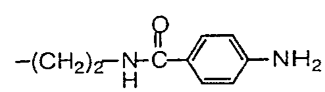
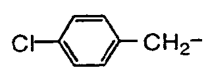
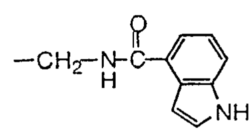
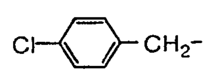
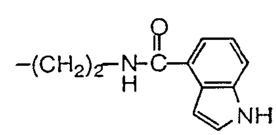
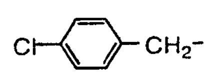
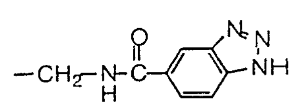
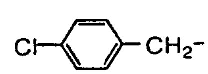
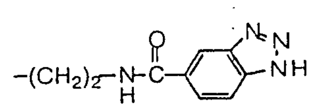
Compd. No.	$R^1R^2{>}(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
969		1	2	0	R	H	
970		1	2	0	R	H	
971		1	2	0	R	H	
972		1	2	0	R	H	
973		1	2	0	R	H	
974		1	2	0	R	H	
975		1	2	0	R	H	
976		1	2	0	R	H	
977		1	2	0	R	H	
978		1	2	0	R	H	
979		1	2	0	R	H	

Table 1.90

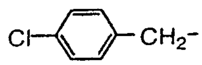
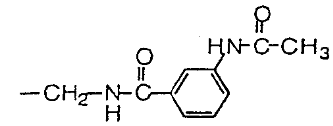
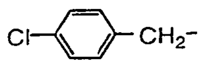
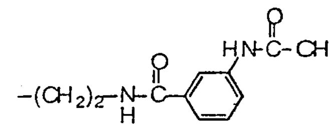
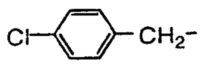
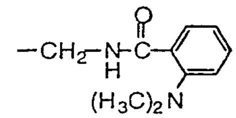
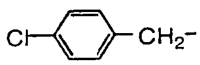
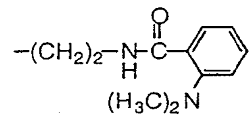
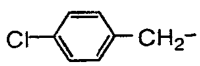
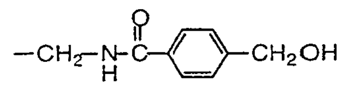
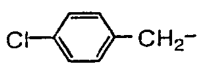
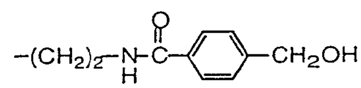
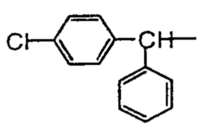
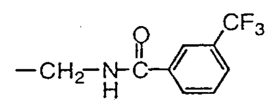
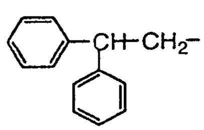
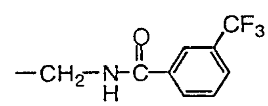
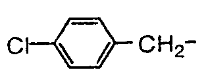
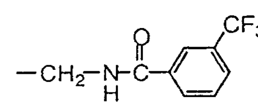
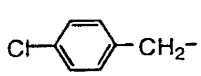
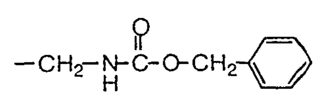
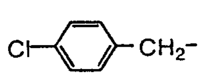
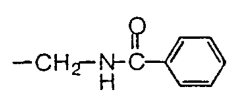
Compd. No.	$\underset{R^2}{\overset{R^1}{>}}-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{\vert}}-(CH_2)_q-G-R^6$
980		1	2	0	R	H	
981		1	2	0	R	H	
982		1	2	0	R	H	
983		1	2	0	R	H	
984		1	2	0	R	H	
985		1	2	0	R	H	
986		1	2	0	R	H	
987		2	2	1	-	H	
988		1	4	0	-	H	
989		1	4	0	-	H	
990		1	4	0	-	H	

Table 1.91

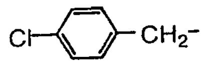
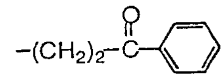
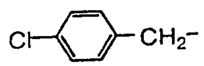
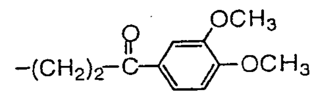
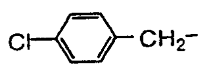
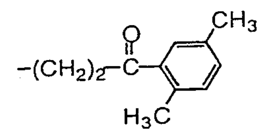
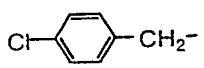
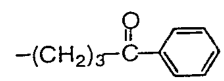
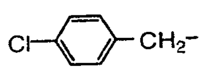
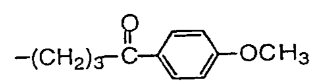
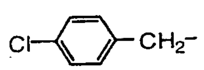
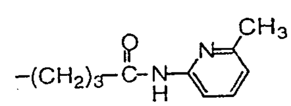
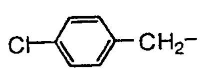
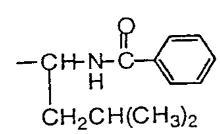
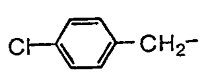
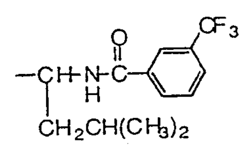
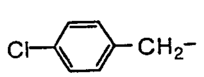
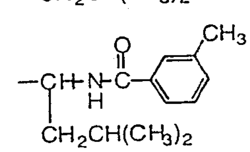
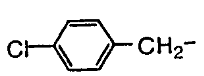
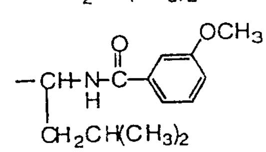
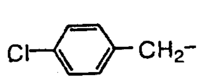
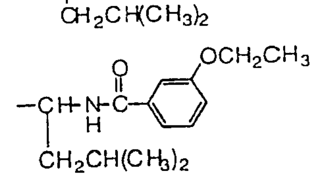
Compd. No.	R^1R^2>$(CH_2)_j$–	k	m	n	chirality	R^3	–$(CH_2)_p$–$C(R^4)(R^5)$–$(CH_2)_q$–G–R^6
991		1	4	0	-	H	
992		1	4	0	-	H	
993		1	4	0	-	H	
994		1	4	0	-	H	
995		1	4	0	-	H	
996		1	4	0	-	H	
997		2	2	1	-	H	
998		2	2	1	-	H	
999		2	2	1	-	H	
1000		2	2	1	-	H	
1001		2	2	1	-	H	

Table 1.92

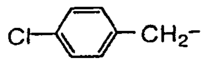
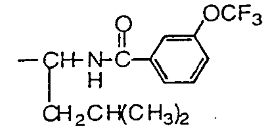
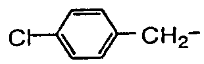
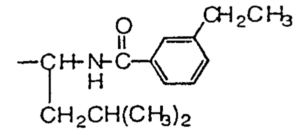
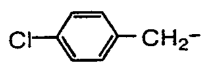
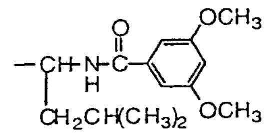
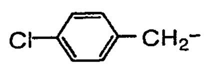
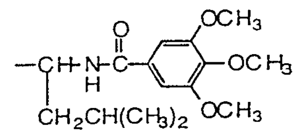
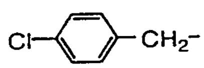
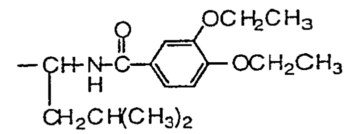
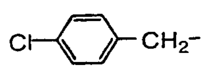
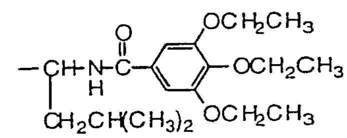
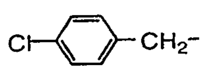
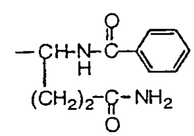
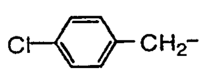
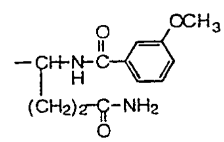
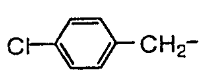
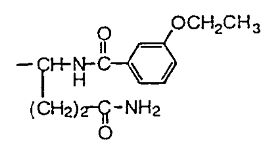
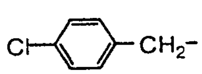
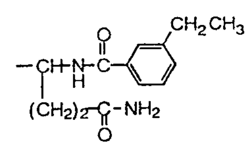
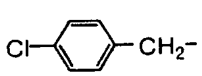
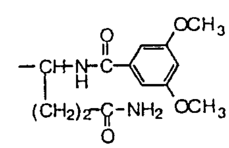
Compd. No.	$R^1R^2>$-$(CH_2)_j$-	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1002		2	2	1	-	H	
1003		2	2	1	-	H	
1004		2	2	1	-	H	
1005		2	2	1	-	H	
1006		2	2	1	-	H	
1007		2	2	1	-	H	
1008		2	2	1	-	H	
1009		2	2	1	-	H	
1010		2	2	1	-	H	
1011		2	2	1	-	H	
1012		2	2	1	-	H	

Table 1.93

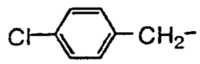
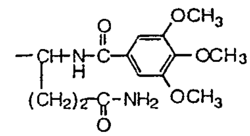
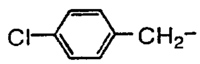
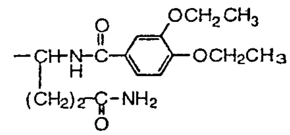
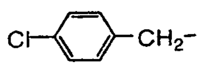
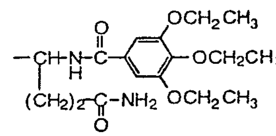
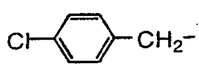
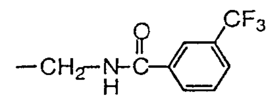
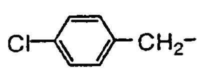
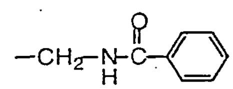
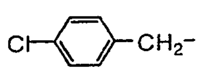
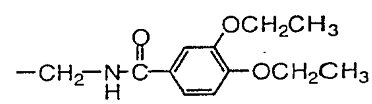
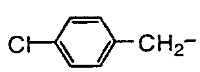
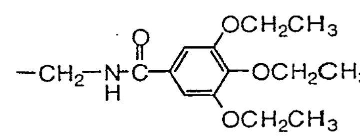
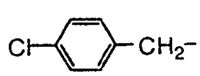
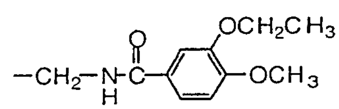
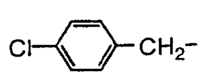
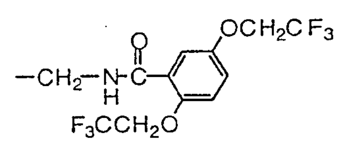
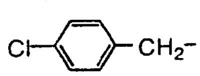
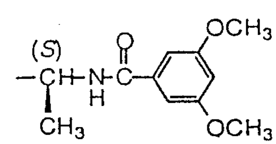
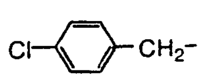
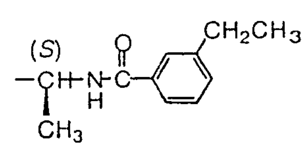
Compd. No.	R^1R^2>-$(CH_2)_j$–	k	m	n	chirality	R^3	–$(CH_2)_p$–$C(R^4)(R^5)$–$(CH_2)_q$–G–R^6
1013		2	2	1	-	H	
1014		2	2	1	-	H	
1015		2	2	1	-	H	
1016		2	2	0	-	H	
1017		2	2	0	-	H	
1018		2	2	1	-	H	
1019		2	2	1	-	H	
1020		2	2	1	-	H	
1021		2	2	1	-	H	
1022		2	2	1	-	H	
1023		2	2	1	-	H	

Table 1.94

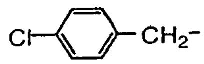
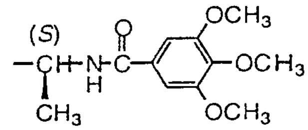
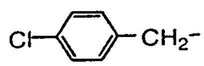
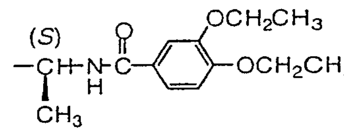
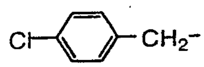
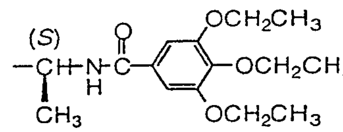
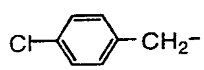
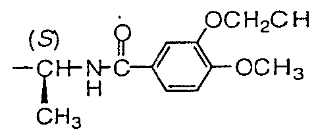
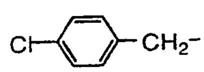
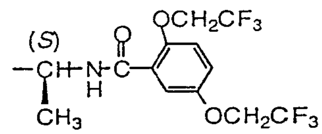
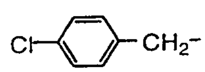
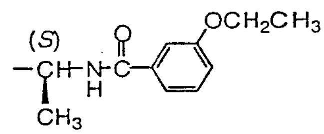
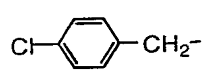
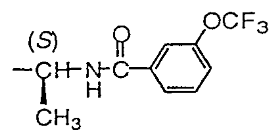
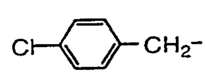
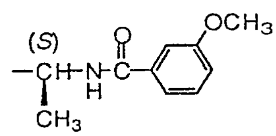
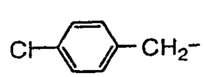
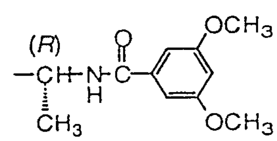
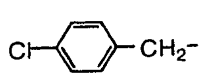
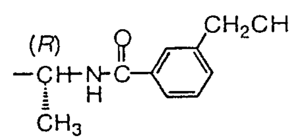
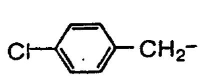
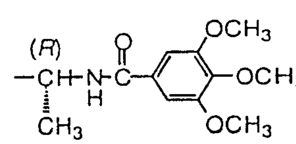
Compd. No.	$R^1R^2>-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1024		2	2	1	-	H	
1025		2	2	1	-	H	
1026		2	2	1	-	H	
1027		2	2	1	-	H	
1028		2	2	1	-	H	
1029		2	2	1	-	H	
1030		2	2	1	-	H	
1031		2	2	1	-	H	
1032		2	2	1	-	H	
1033		2	2	1	-	H	
1034		2	2	1	-	H	

Table 1.95

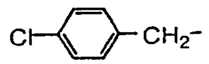
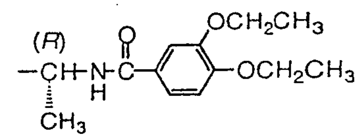
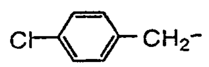
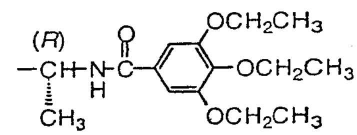
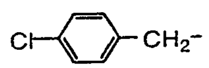
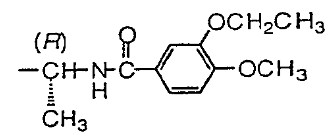
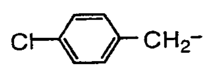
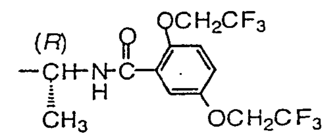
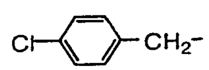
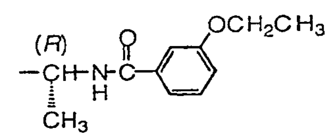
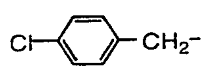
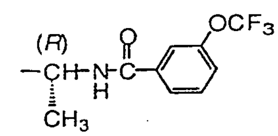
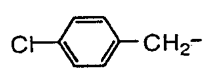
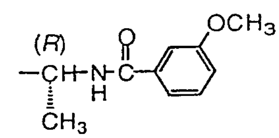
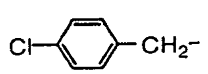
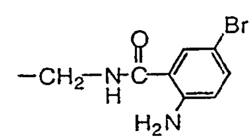
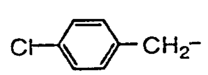
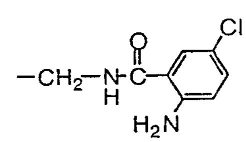
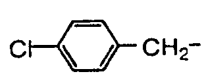
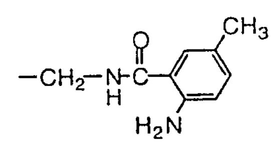
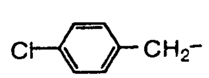
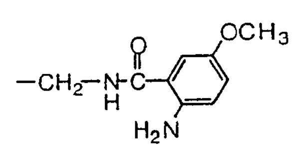
Compd. No.	$R^1R^2>$-$(CH_2)_j$–	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1035		2	2	1	-	H	
1036		2	2	1	-	H	
1037		2	2	1	-	H	
1038		2	2	1	-	H	
1039		2	2	1	-	H	
1040		2	2	1	-	H	
1041		2	2	1	-	H	
1042		2	2	1	-	H	
1043		2	2	1	-	H	
1044		2	2	1	-	H	
1045		2	2	1	-	H	

Table 1.96

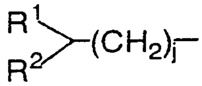
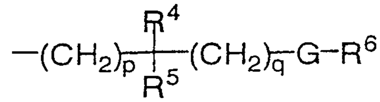
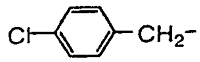
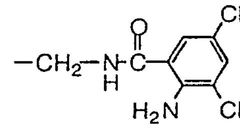
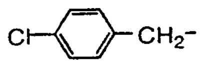
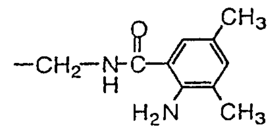
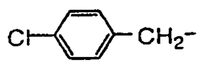
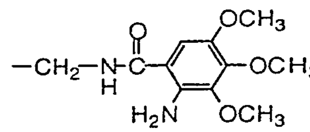
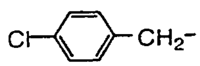
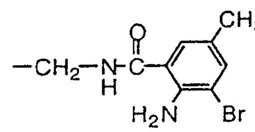
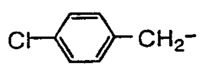
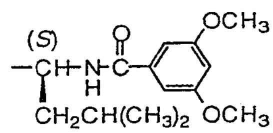
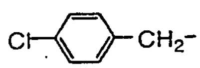
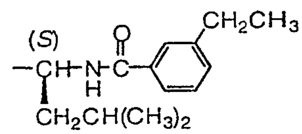
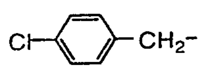
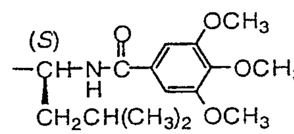
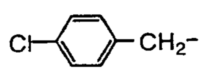
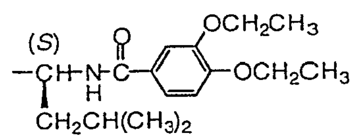
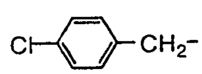
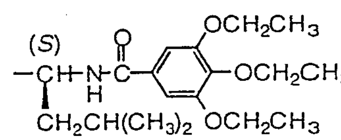
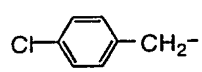
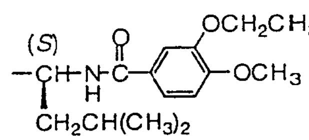
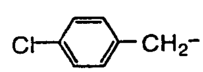
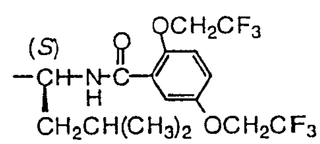
Compd. No.		k	m	n	chirality	R^3	
1046		2	2	1	-	H	
1047		2	2	1	-	H	
1048		2	2	1	-	H	
1049		2	2	1	-	H	
1050		2	2	1	-	H	
1051		2	2	1	-	H	
1052		2	2	1	-	H	
1053		2	2	1	-	H	
1054		2	2	1	-	H	
1055		2	2	1	-	H	
1056		2	2	1	-	H	

Table 1.97

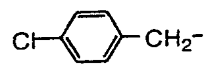
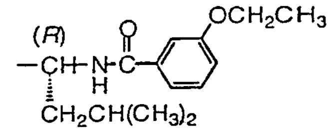
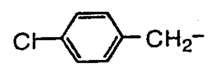
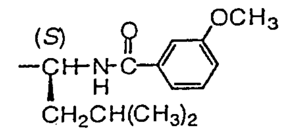
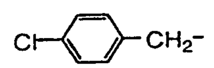
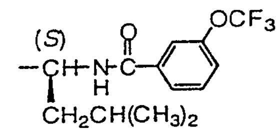
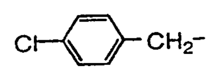
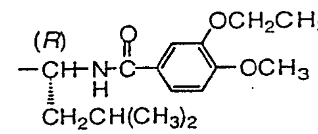
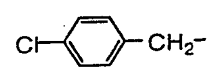
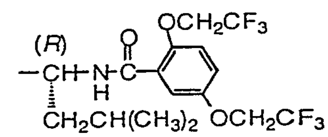
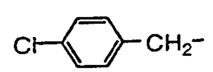
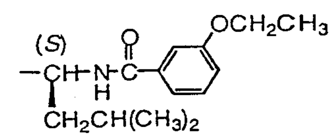
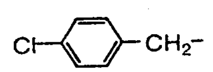
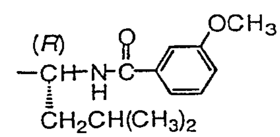
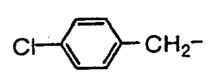
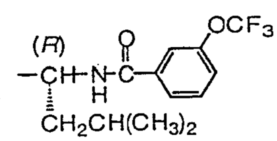
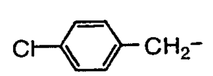
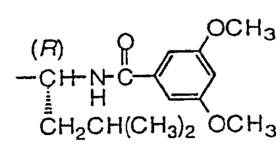
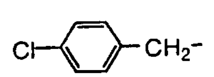
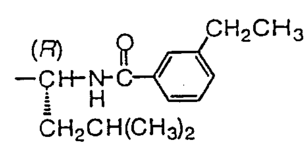
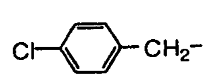
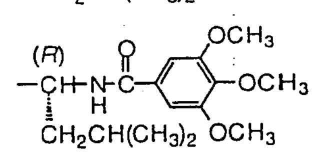
Compd. No.	$R^1R^2>$-$(CH_2)_j$-	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1057		2	2	1	-	H	
1058		2	2	1	-	H	
1059		2	2	1	-	H	
1060		2	2	1	-	H	
1061		2	2	1	-	H	
1062		2	2	1	-	H	
1063		2	2	1	-	H	
1064		2	2	1	-	H	
1065		2	2	1	-	H	
1066		2	2	1	-	H	
1067		2	2	1	-	H	

Table 1.98

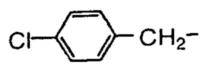
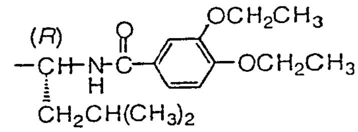
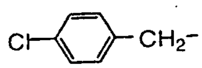
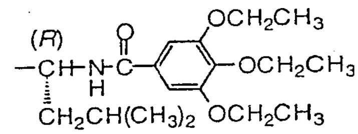
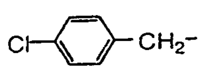
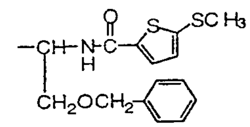
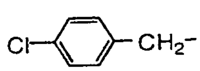
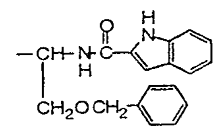
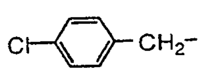
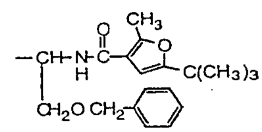
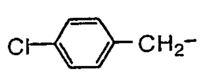
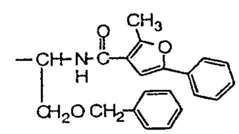
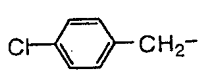
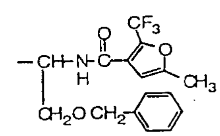
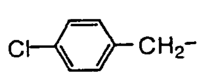
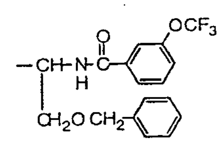
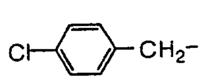
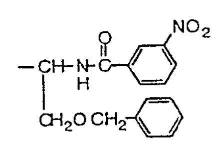
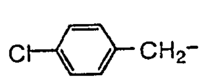
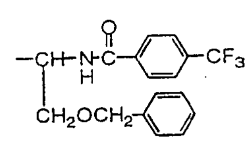
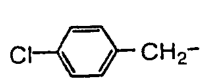
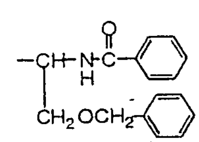
Compd. No.	$R^1R^2>$—$(CH_2)_j$—	k	m	n	chirality	R^3	—$(CH_2)_p$—$C(R^4)(R^5)$—$(CH_2)_q$—G—R^6
1068		2	2	1	-	H	
1069		2	2	1	-	H	
1070		2	2	1	-	H	
1071		2	2	1	-	H	
1072		2	2	1	-	H	
1073		2	2	1	-	H	
1074		2	2	1	-	H	
1075		2	2	1	-	H	
1076		2	2	1	-	H	
1077		2	2	1	-	H	
1078		2	2	1	-	H	

Table 1.99

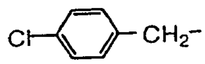
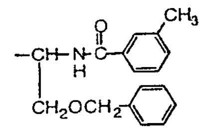
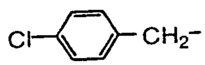
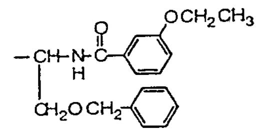
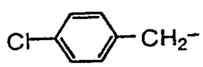
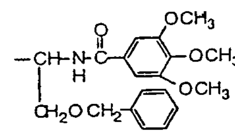
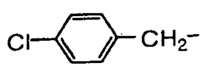
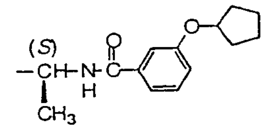
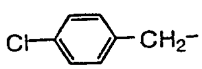
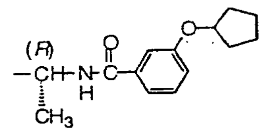
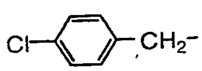
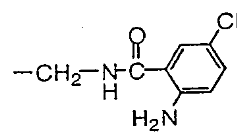
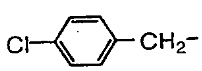
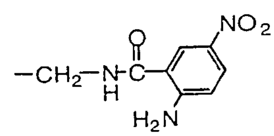
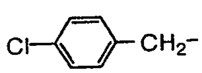
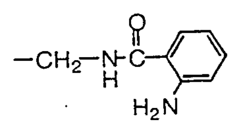
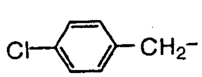
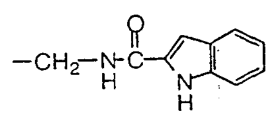
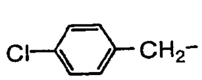
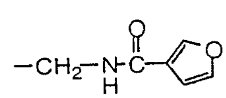
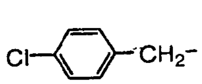
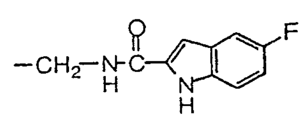
Compd. No.	R^1R^2>$(CH_2)_j$–	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1079		2	2	1	-	H	
1080		2	2	1	-	H	
1081		2	2	1	-	H	
1082		2	2	1	-	H	
1083		2	2	1	-	H	
1084		1	2	0	R	H	
1085		1	2	0	R	H	
1086		1	2	0	R	H	
1087		1	2	0	R	H	
1088		1	2	0	R	H	
1089		1	2	0	R	H	

Table 1.100

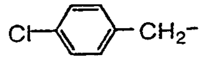
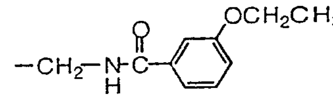
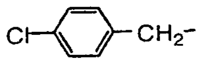
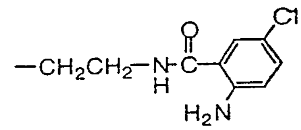
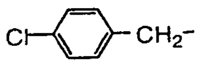
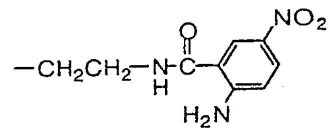
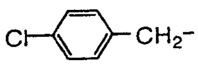
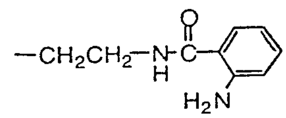
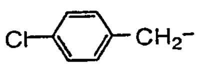
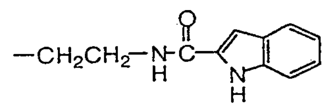
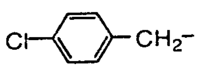
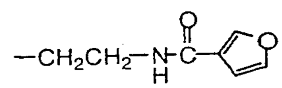
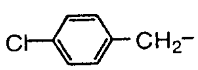
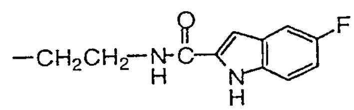
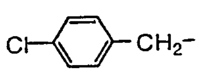
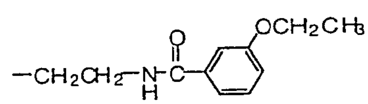
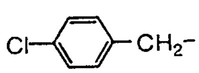
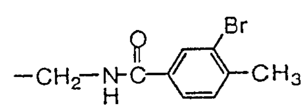
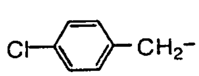
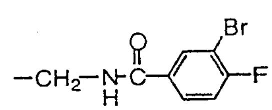
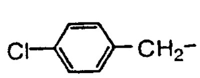
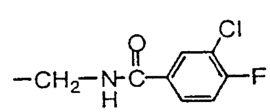
Compd. No.	$R^1R^2>-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1090		1	2	0	R	H	
1091		1	2	0	R	H	
1092		1	2	0	R	H	
1093		1	2	0	R	H	
1094		1	2	0	R	H	
1095		1	2	0	R	H	
1096		1	2	0	R	H	
1097		1	2	0	R	H	
1098		1	2	0	R	H	
1099		1	2	0	R	H	
1100		1	2	0	R	H	

Table 1.101

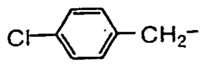
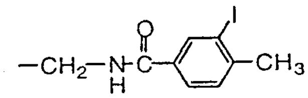
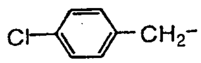
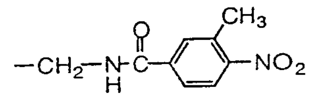
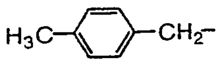
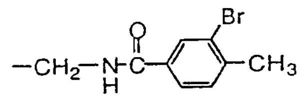
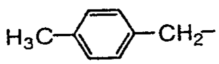
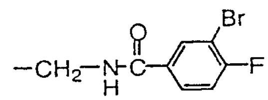
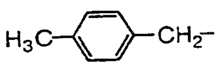
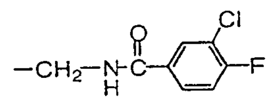
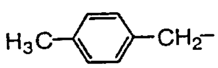
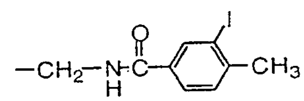
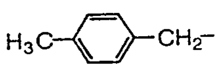
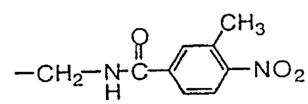
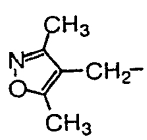
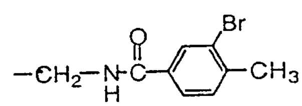
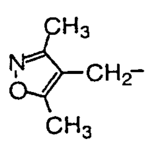
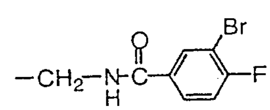
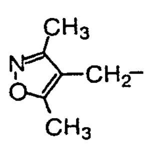
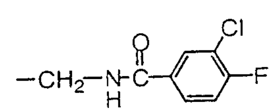
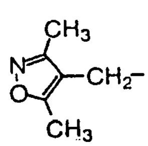
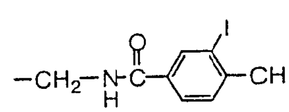
Compd. No.	$R^1R^2{>}(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1101		1	2	0	R	H	
1102		1	2	0	R	H	
1103		1	2	0	R	H	
1104		1	2	0	R	H	
1105		1	2	0	R	H	
1106		1	2	0	R	H	
1107		1	2	0	R	H	
1108		1	2	0	R	H	
1109		1	2	0	R	H	
1110		1	2	0	R	H	
1111		1	2	0	R	H	

Table 1.102

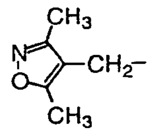
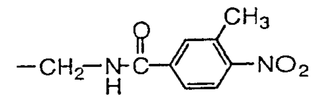
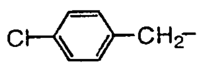
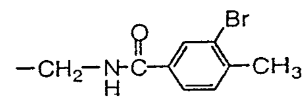
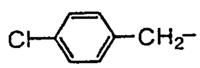
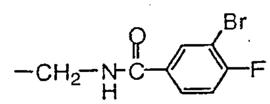
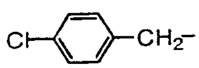
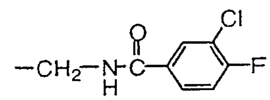
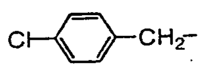
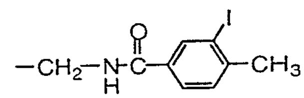
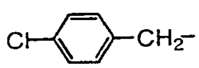
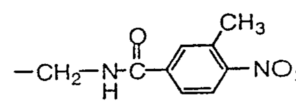
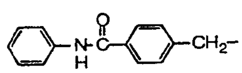
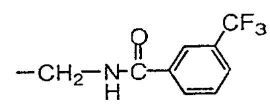
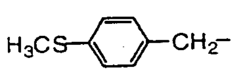
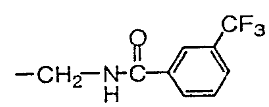
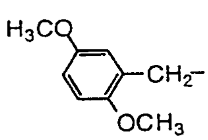
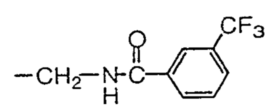
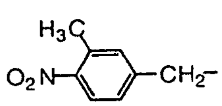
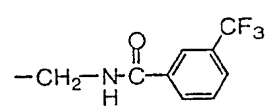
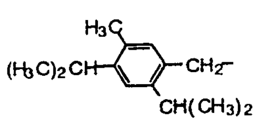
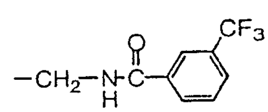
Compd. No.	R^1R^2>-$(CH_2)_j$-	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1112		1	2	0	R	H	
1113		2	2	1	-	H	
1114		2	2	1	-	H	
1115		2	2	1	-	H	
1116		2	2	1	-	H	
1117		2	2	1	-	H	
1118		1	2	0	R	H	
1119		1	2	0	R	H	
1120		1	2	0	R	H	
1121		1	2	0	R	H	
1122		1	2	0	R	H	

Table 1.103

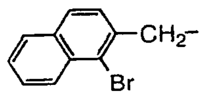
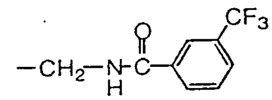
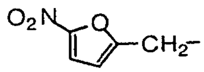
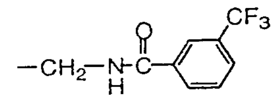
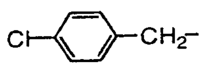
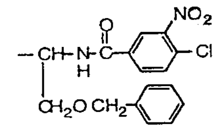
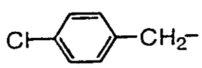
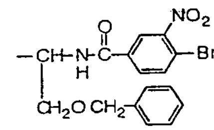
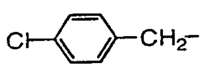
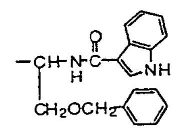
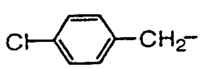
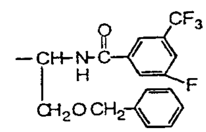
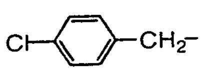
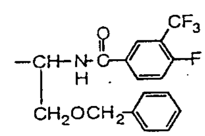
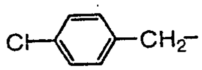
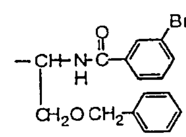
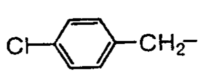
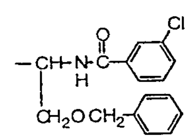
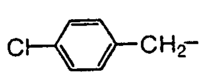
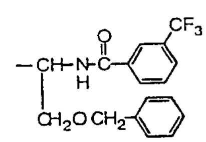
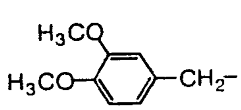
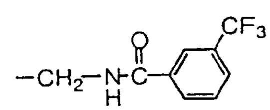
Compd. No.	$R^1R^2>$-$(CH_2)_j$-	k	m	n	chirality	R^3	-$(CH_2)_p$-$C(R^4)(R^5)$-$(CH_2)_q$-G-R^6
1123		1	2	0	R	H	
1124		1	2	0	R	H	
1125		2	2	1	-	H	
1126		2	2	1	-	H	
1127		2	2	1	-	H	
1128		2	2	1	-	H	
1129		2	2	1	-	H	
1130		2	2	1	-	H	
1131		2	2	1	-	H	
1132		2	2	1	-	H	
1133		1	2	0	R	H	

Table 1.104

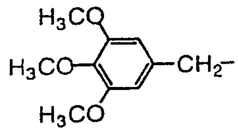
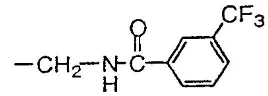
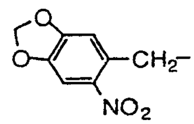
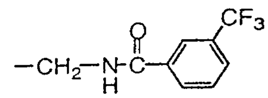
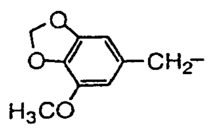
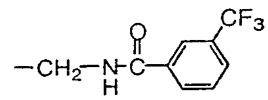
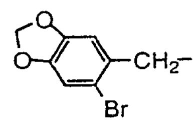
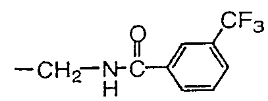
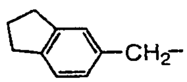
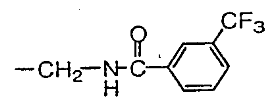
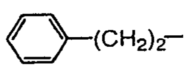
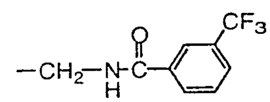
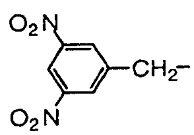
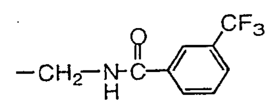
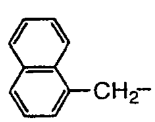
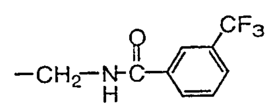
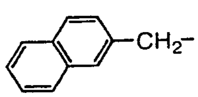
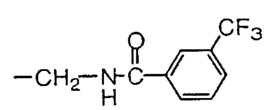
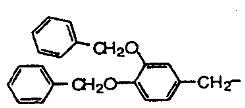
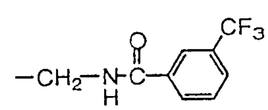
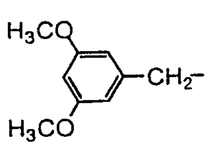
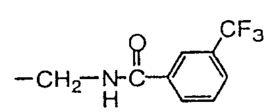
Compd. No.	$R^1R^2>$—$(CH_2)_j$—	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1134		1	2	0	R	H	
1135		1	2	0	R	H	
1136		1	2	0	R	H	
1137		1	2	0	R	H	
1138		1	2	0	R	H	
1139		1	2	0	R	H	
1140		1	2	0	R	H	
1141		1	2	0	R	H	
1142		1	2	0	R	H	
1143		1	2	0	R	H	
1144		1	2	0	R	H	

Table 1.105

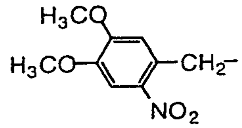
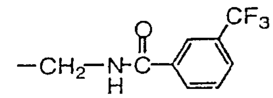
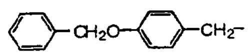
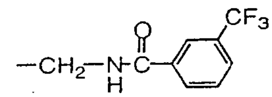
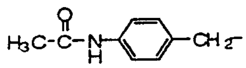
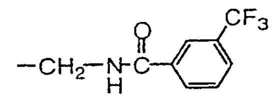
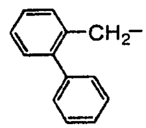
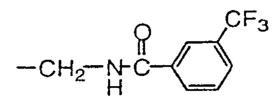
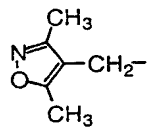
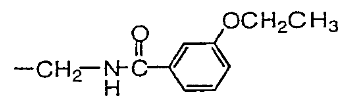
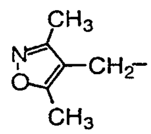
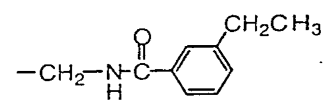
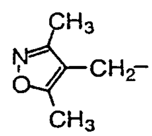
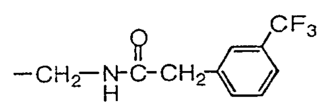
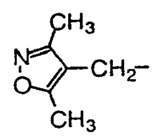
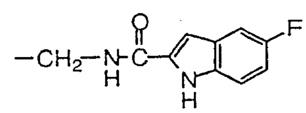
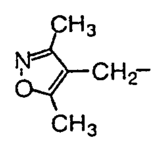
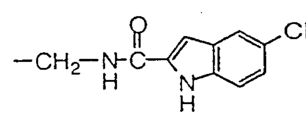
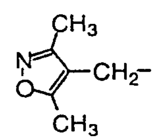
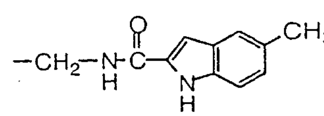
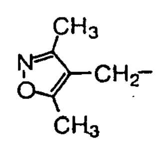
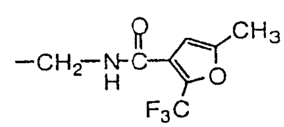
Compd. No.	$R^1R^2>-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1145		1	2	0	R	H	
1146		1	2	0	R	H	
1147		1	2	0	R	H	
1148		1	2	0	R	H	
1149		1	2	0	R	H	
1150		1	2	0	R	H	
1151		1	2	0	R	H	
1152		1	2	0	R	H	
1153		1	2	0	R	H	
1154		1	2	0	R	H	
1155		1	2	0	R	H	

Table 1.106

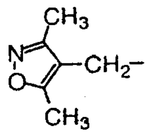
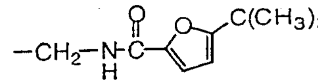
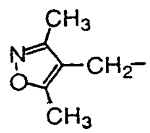
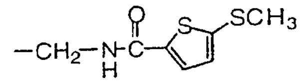
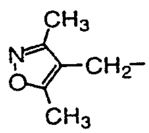
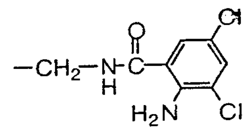
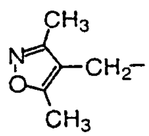
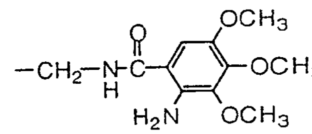
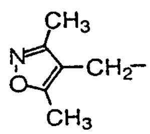
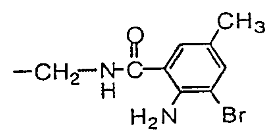
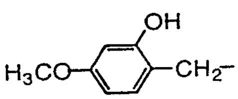
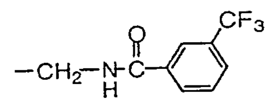
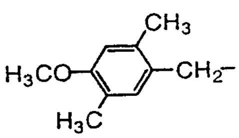
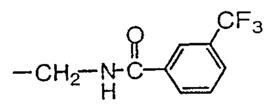
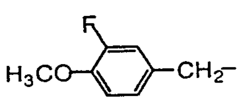
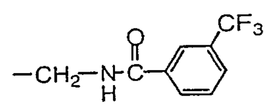
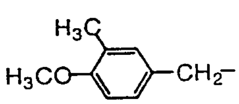
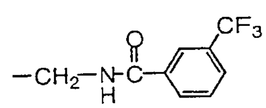
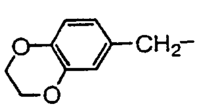
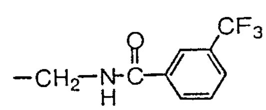
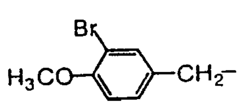
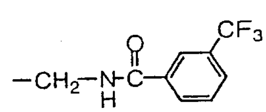
Compd. No.	$R^1R^2{>}\text{-}(CH_2)_j\text{-}$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1156		1	2	0	R	H	
1157		1	2	0	R	H	
1158		1	2	0	R	H	
1159		1	2	0	R	H	
1160		1	2	0	R	H	
1161		1	2	0	R	H	
1162		1	2	0	R	H	
1163		1	2	0	R	H	
1164		1	2	0	R	H	
1165		1	2	0	R	H	
1166		1	2	0	R	H	

Table 1.107

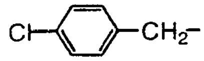
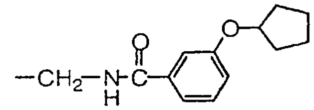
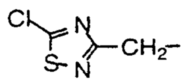
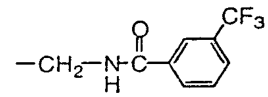
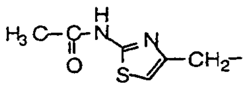
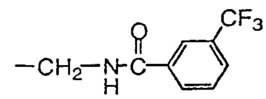
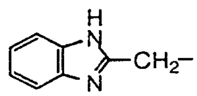
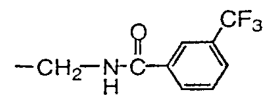
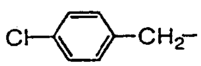
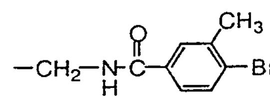
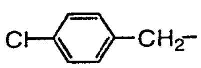
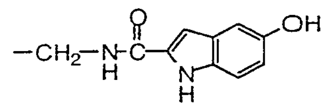
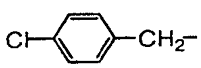
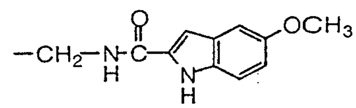
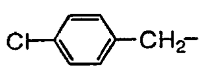
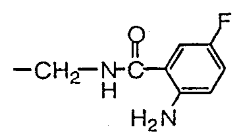
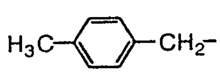
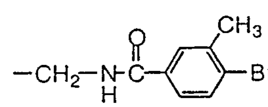
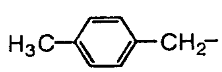
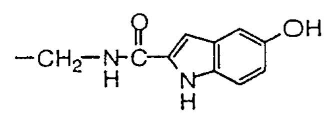
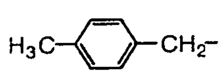
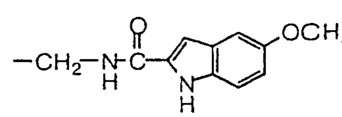
Compd. No.	R^1R^2>-$(CH_2)_j$–	k	m	n	chirality	R^3	–$(CH_2)_p$–$C(R^4)(R^5)$–$(CH_2)_q$–G–R^6
1167		2	2	1	-	H	
1168		1	2	0	R	H	
1169		1	2	0	R	H	
1170		1	2	0	R	H	
1171		1	2	0	R	H	
1172		1	2	0	R	H	
1173		1	2	0	R	H	
1174		1	2	0	R	H	
1175		1	2	0	R	H	
1176		1	2	0	R	H	
1177		1	2	0	R	H	

Table 1.108

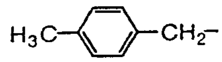
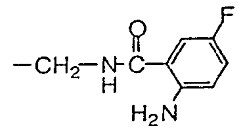
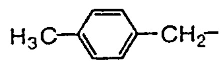
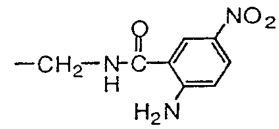
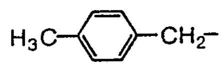
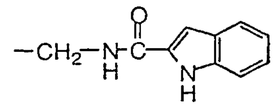
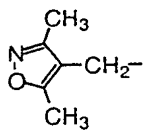
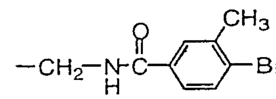
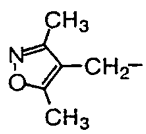
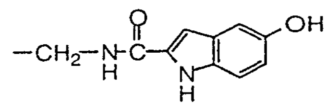
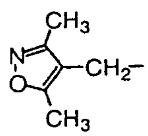
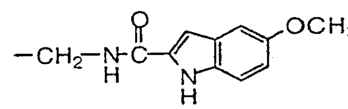
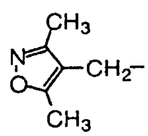
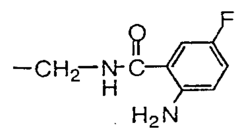
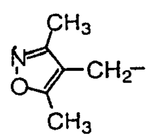
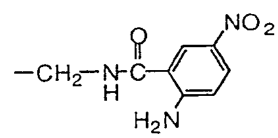
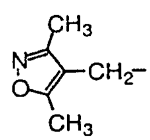
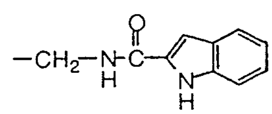
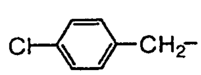
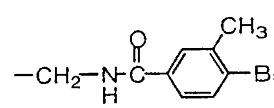
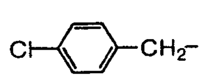
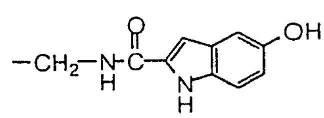
Compd. No.	$R^1R^2>$–$(CH_2)_j$–	k	m	n	chirality	R^3	–$(CH_2)_p$–$C(R^4)(R^5)$–$(CH_2)_q$–G–R^6
1178		1	2	0	R	H	
1179		1	2	0	R	H	
1180		1	2	0	R	H	
1181		1	2	0	R	H	
1182		1	2	0	R	H	
1183		1	2	0	R	H	
1184		1	2	0	R	H	
1185		1	2	0	R	H	
1186		1	2	0	R	H	
1187		2	2	1	-	H	
1188		2	2	1	-	H	

Table 1.109

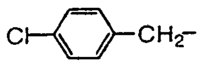
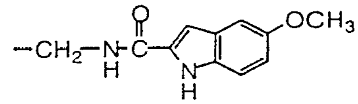
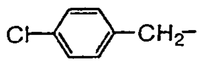
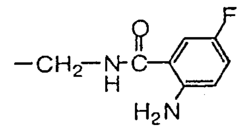
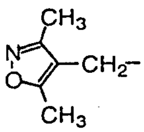
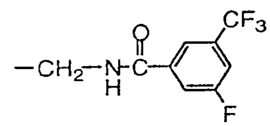
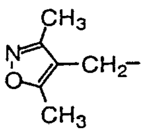
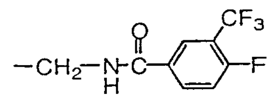
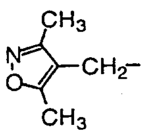
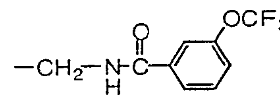
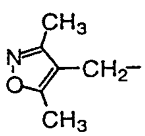
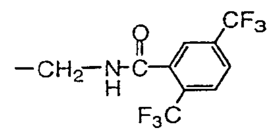
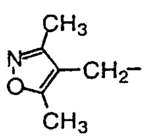
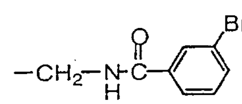
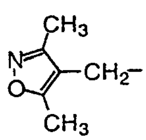
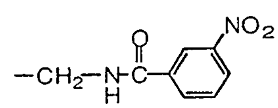
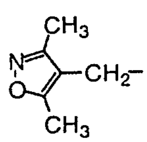
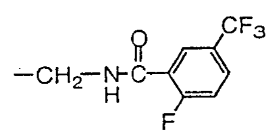
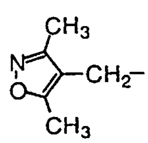
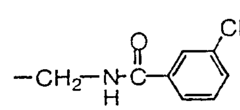
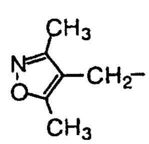
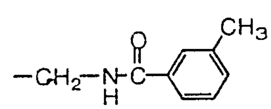
Compd. No.	$R^1R^2>$-$(CH_2)_j$-	k	m	n	chirality	R^3	-$(CH_2)_p$-$C(R^4)(R^5)$-$(CH_2)_q$-G-R^6
1189		2	2	1	-	H	
1190		2	2	1	-	H	
1191		1	2	0	R	H	
1192		1	2	0	R	H	
1193		1	2	0	R	H	
1194		1	2	0	R	H	
1195		1	2	0	R	H	
1196		1	2	0	R	H	
1197		1	2	0	R	H	
1198		1	2	0	R	H	
1199		1	2	0	R	H	

Table 1.110

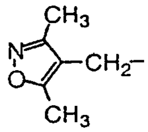
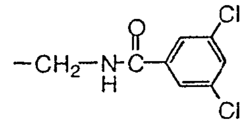
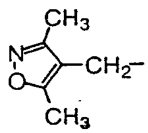
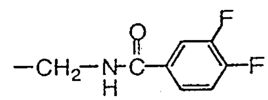
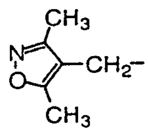
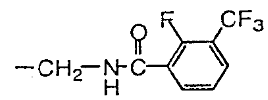
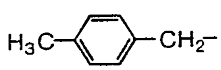
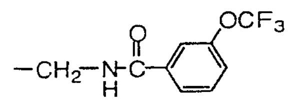
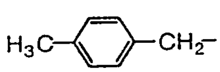
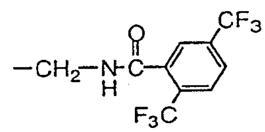
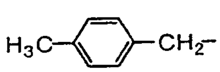
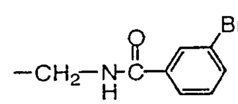
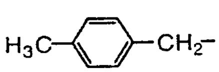
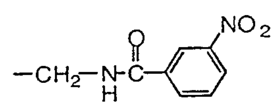
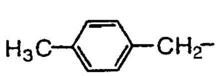
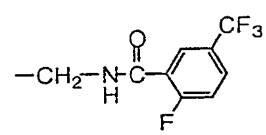
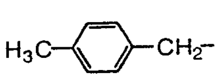
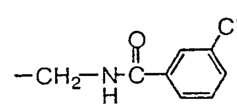
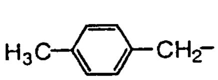
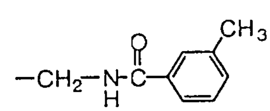
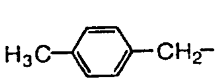
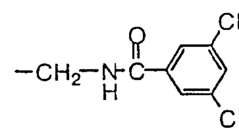
Compd. No.	$R^1R^2>(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1200		1	2	0	R	H	
1201		1	2	0	R	H	
1202		1	2	0	R	H	
1203		1	2	0	R	H	
1204		1	2	0	R	H	
1205		1	2	0	R	H	
1206		1	2	0	R	H	
1207		1	2	0	R	H	
1208		1	2	0	R	H	
1209		1	2	0	R	H	
1210		1	2	0	R	H	

Table 1.111

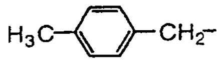
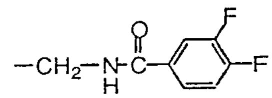
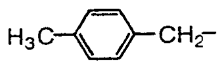
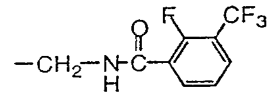
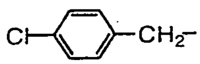
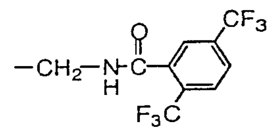
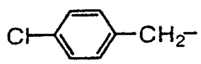
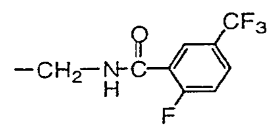
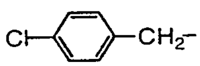
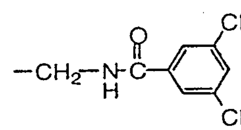
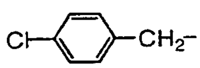
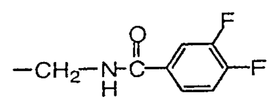
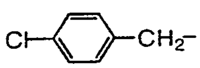
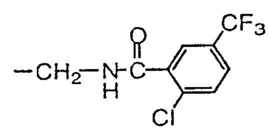
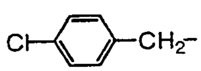
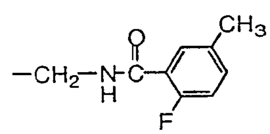
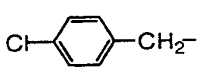
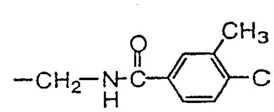
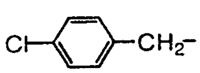
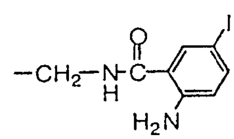
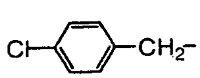
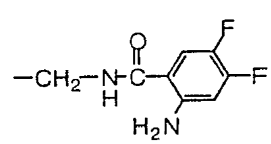
Compd. No.	$R^1R^2>$-$(CH_2)_j$–	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1211		1	2	0	R	H	
1212		1	2	0	R	H	
1213		2	2	1	-	H	
1214		2	2	1	-	H	
1215		2	2	1	-	H	
1216		2	2	1	-	H	
1217		1	2	0	R	H	
1218		1	2	0	R	H	
1219		1	2	0	R	H	
1220		1	2	0	R	H	
1221		1	2	0	R	H	

Table 1.112

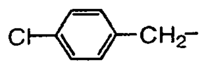
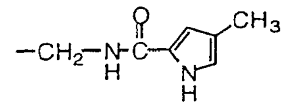
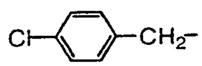
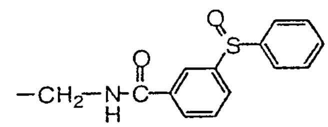
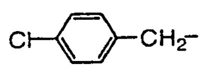
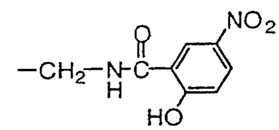
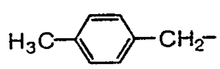
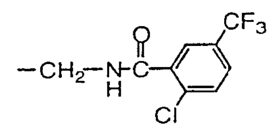
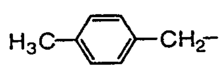
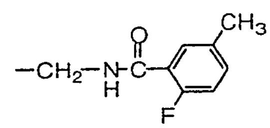
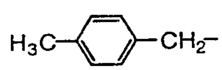
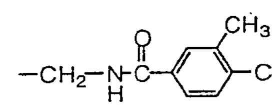
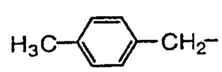
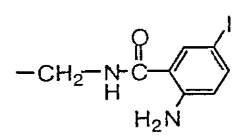
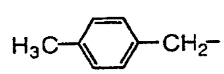
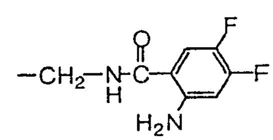
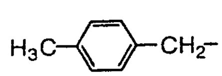
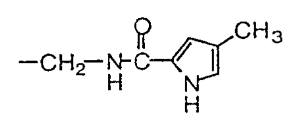
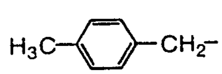
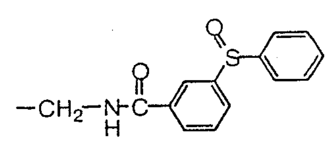
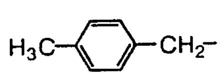
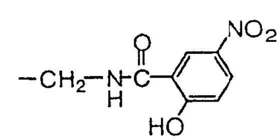
Compd. No.	$R^1R^2{>}\text{-}(CH_2)_j\text{-}$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1222		1	2	0	R	H	
1223		1	2	0	R	H	
1224		1	2	0	R	H	
1225		1	2	0	R	H	
1226		1	2	0	R	H	
1227		1	2	0	R	H	
1228		1	2	0	R	H	
1229		1	2	0	R	H	
1230		1	2	0	R	H	
1231		1	2	0	R	H	
1232		1	2	0	R	H	

Table 1.113

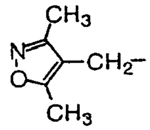
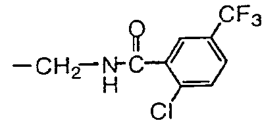
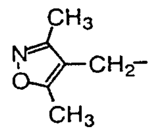
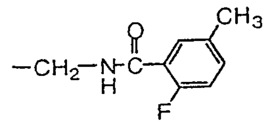
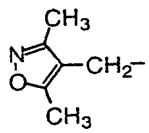
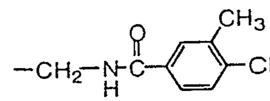
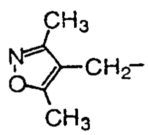
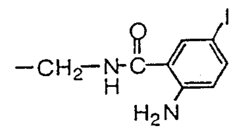
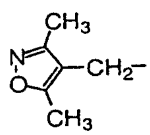
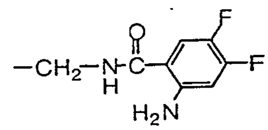
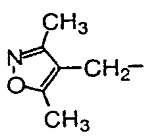
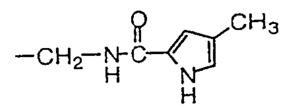
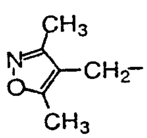
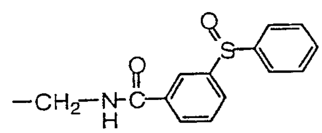
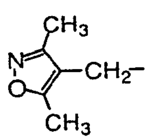
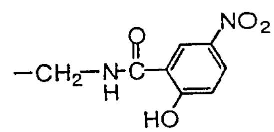
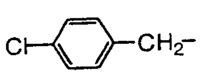
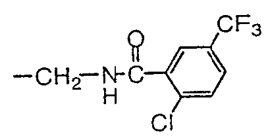
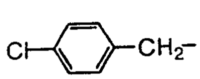
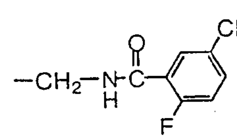
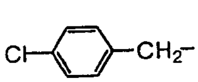
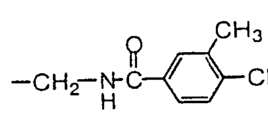
Compd. No.	R^1R^2>$-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1233		1	2	0	R	H	
1234		1	2	0	R	H	
1235		1	2	0	R	H	
1236		1	2	0	R	H	
1237		1	2	0	R	H	
1238		1	2	0	R	H	
1239		1	2	0	R	H	
1240		1	2	0	R	H	
1241		2	2	1	-	H	
1242		2	2	1	-	H	
1243		2	2	1	-	H	

Table 1.114

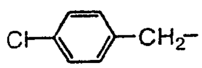
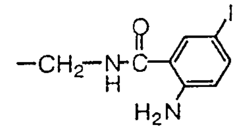
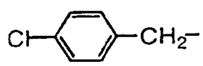
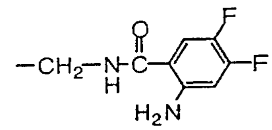
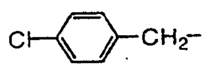
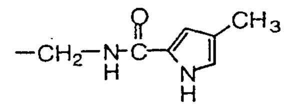
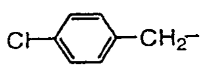
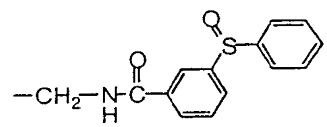
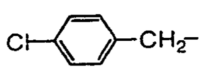
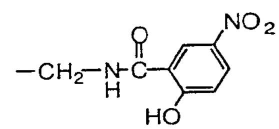
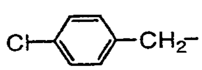
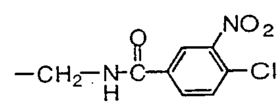
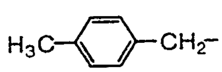
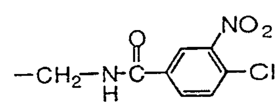
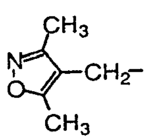
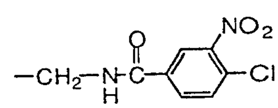
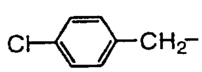
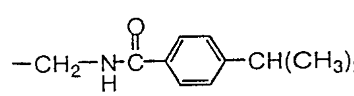
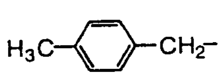
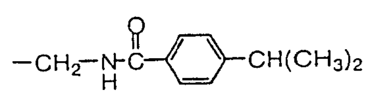
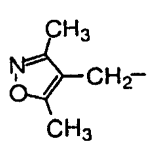
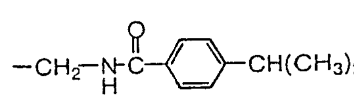
Compd. No.	$R^1R^2>$(CH$_2$)$_j$–	k	m	n	chirality	R^3	–(CH$_2$)$_p$–C(R^4)(R^5)–(CH$_2$)$_q$–G–R^6
1244		2	2	1	-	H	
1245		2	2	1	-	H	
1246		2	2	1	-	H	
1247		2	2	1	-	H	
1248		2	2	1	-	H	
1249		1	2	0	R	H	
1250		1	2	0	R	H	
1251		1	2	0	R	H	
1252		1	2	0	R	H	
1253		1	2	0	R	H	
1254		1	2	0	R	H	

Table 1.115

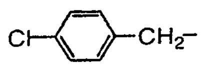
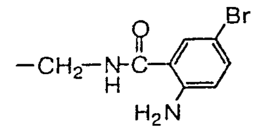
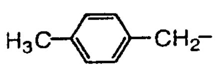
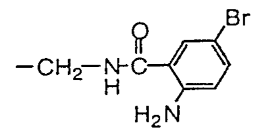
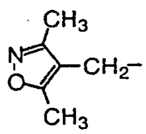
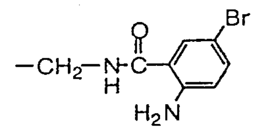
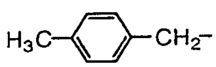
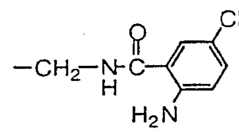
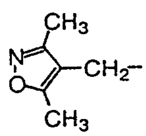
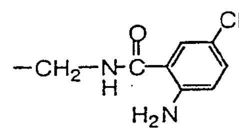
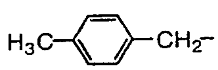
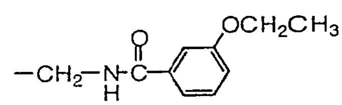
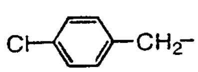
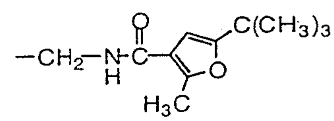
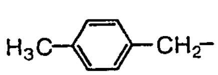
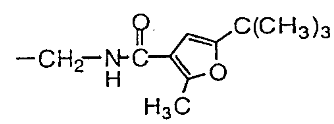
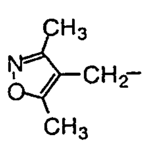
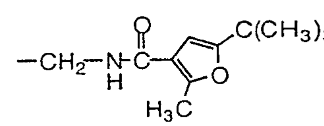
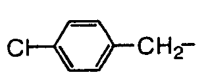
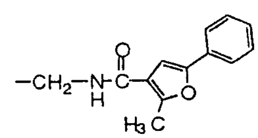
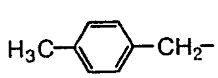
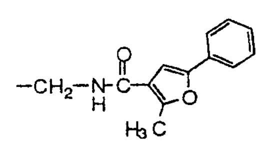
Compd. No.	$R^1R^2>$-$(CH_2)_j$-	k	m	n	chirality	R^3	-$(CH_2)_p$-$C(R^4)(R^5)$-$(CH_2)_q$-G-R^6
1255		1	2	0	R	H	
1256		1	2	0	R	H	
1257		1	2	0	R	H	
1258		1	2	0	R	H	
1259		1	2	0	R	H	
1260		1	2	0	R	H	
1261		1	2	0	R	H	
1262		1	2	0	R	H	
1263		1	2	0	R	H	
1264		1	2	0	R	H	
1265		1	2	0	R	H	

Table 1.116

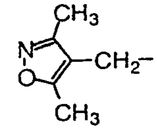
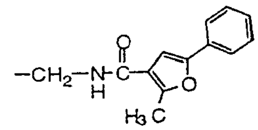
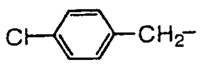
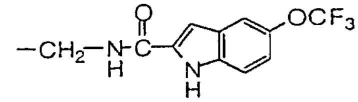
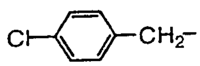
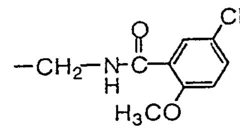
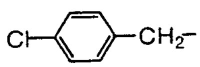
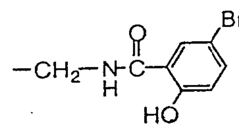
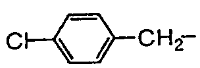
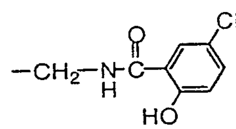
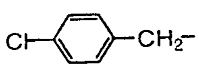
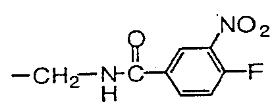
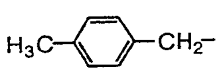
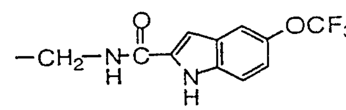
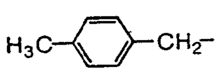
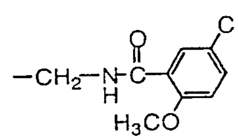
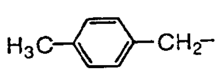
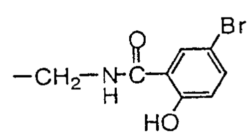
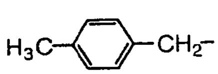
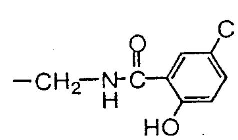
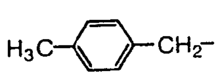
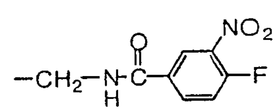
Compd. No.	$R^1R^2>-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1266		1	2	0	R	H	
1267		1	2	0	R	H	
1268		1	2	0	R	H	
1269		1	2	0	R	H	
1270		1	2	0	R	H	
1271		1	2	0	R	H	
1272		1	2	0	R	H	
1273		1	2	0	R	H	
1274		1	2	0	R	H	
1275		1	2	0	R	H	
1276		1	2	0	R	H	

Table 1.117

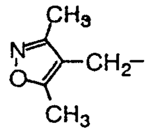
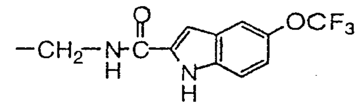
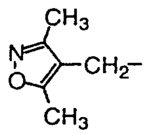
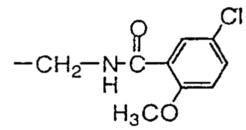
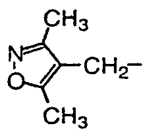
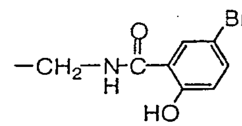
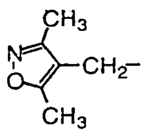
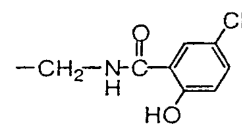
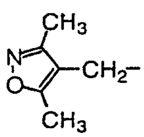
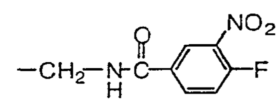
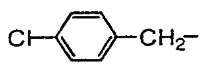
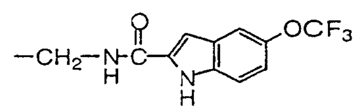
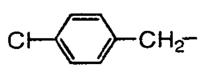
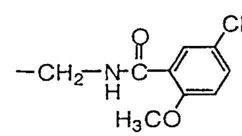
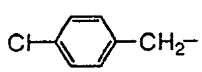
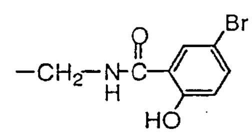
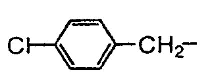
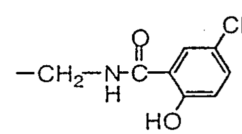
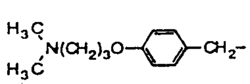
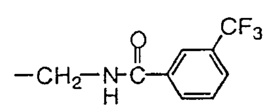
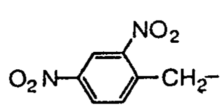
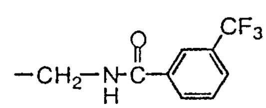
Compd. No.	R^1R^2>$(CH_2)_j$—	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1277		1	2	0	R	H	
1278		1	2	0	R	H	
1279		1	2	0	R	H	
1280		1	2	0	R	H	
1281		1	2	0	R	H	
1282		2	2	1	-	H	
1283		2	2	1	-	H	
1284		2	2	1	-	H	
1285		2	2	1	-	H	
1286		1	2	0	R	H	
1287		1	2	0	R	H	

Table 1.118

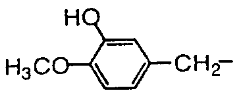
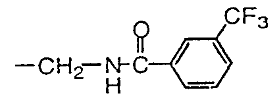
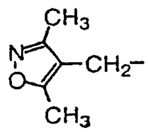
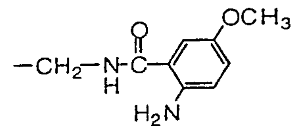
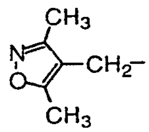
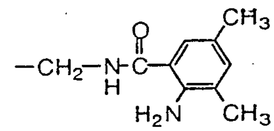
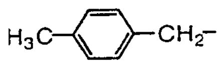
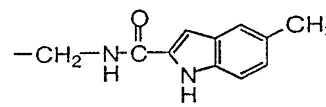
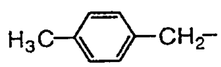
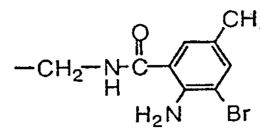
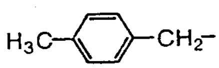
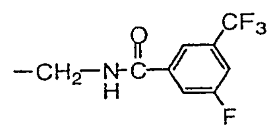
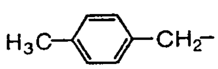
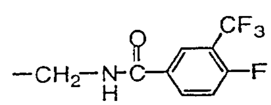
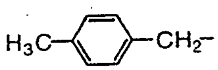
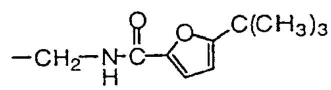
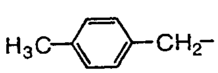
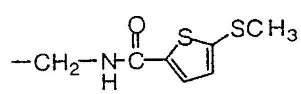
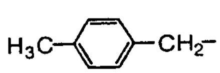
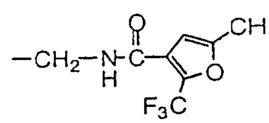
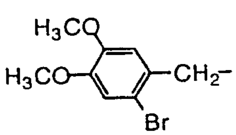
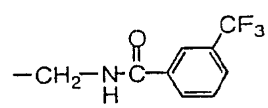
Compd. No.	R^1, R^2 $>$–$(CH_2)_j$–	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1288		1	2	0	R	H	
1289		1	2	0	R	H	
1290		1	2	0	R	H	
1291		1	2	0	R	H	
1292		1	2	0	R	H	
1293		1	2	0	R	H	
1294		1	2	0	R	H	
1295		1	2	0	R	H	
1296		1	2	0	R	H	
1297		1	2	0	R	H	
1298		1	2	0	R	H	

Table 1.119

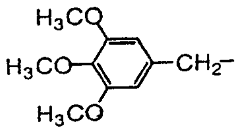
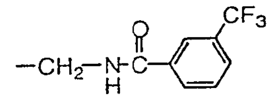
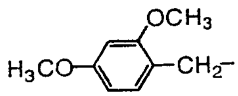
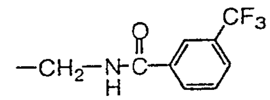
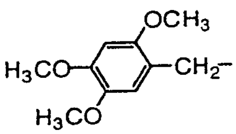
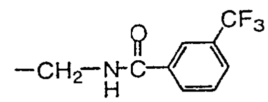
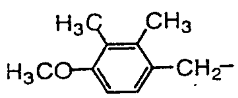
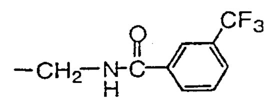
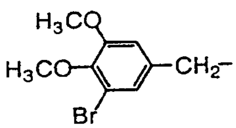
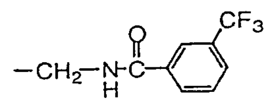
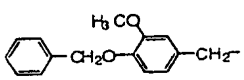
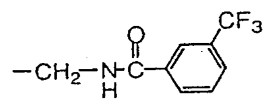
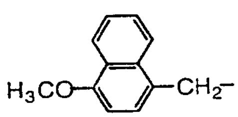
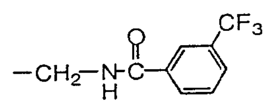
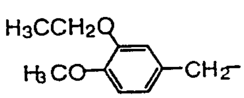
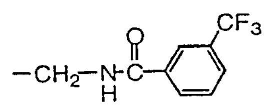
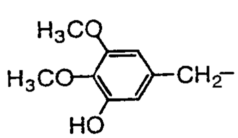
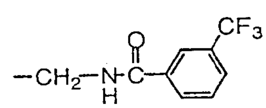
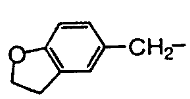
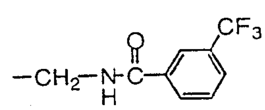
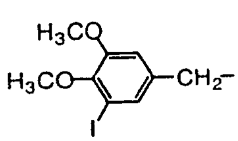
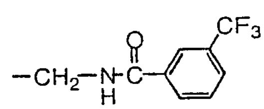
Compd. No.	$R^1R^2>-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1299		1	2	0	R	H	
1300		1	2	0	R	H	
1301		1	2	0	R	H	
1302		1	2	0	R	H	
1303		1	2	0	R	H	
1304		1	2	0	R	H	
1305		1	2	0	R	H	
1306		1	2	0	R	H	
1307		1	2	0	R	H	
1308		1	2	0	R	H	
1309		1	2	0	R	H	

Table 1.120

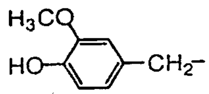
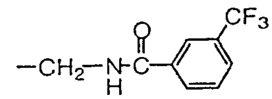
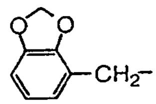
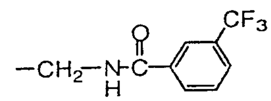
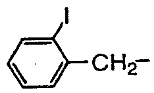
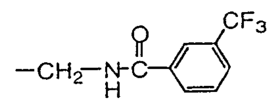
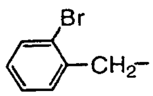
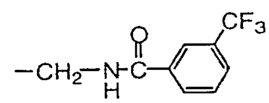
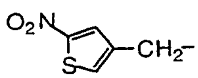
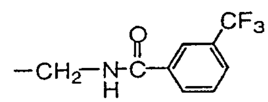
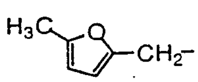
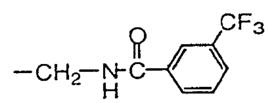
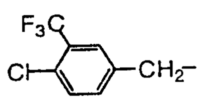
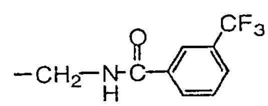
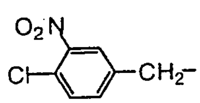
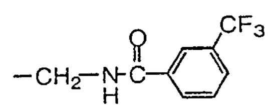
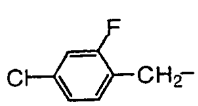
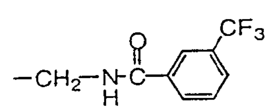
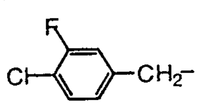
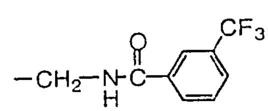
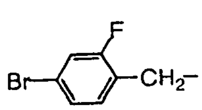
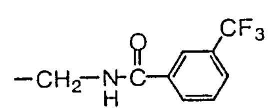
Compd. No.	$R^1R^2>$—$(CH_2)_j$—	k	m	n	chirality	R^3	—$(CH_2)_p$—$C(R^4)(R^5)$—$(CH_2)_q$—G—R^6
1310		1	2	0	R	H	
1311		1	2	0	R	H	
1312		1	2	0	R	H	
1313		1	2	0	R	H	
1314		1	2	0	R	H	
1315		1	2	0	R	H	
1316		1	2	0	R	H	
1317		1	2	0	R	H	
1318		1	2	0	R	H	
1319		1	2	0	R	H	
1320		1	2	0	R	H	

Table 1.121

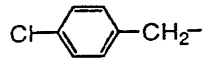
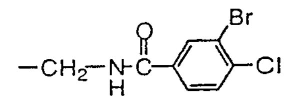
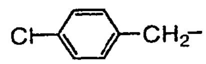
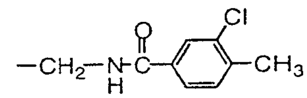
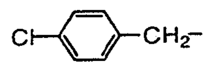
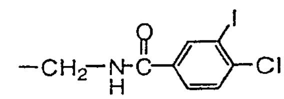
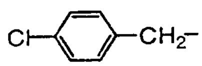
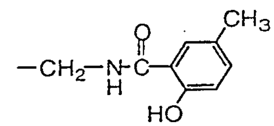
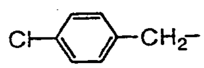
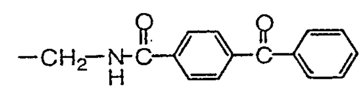
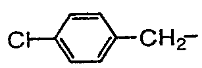
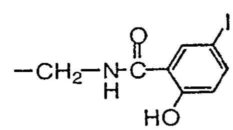
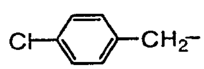
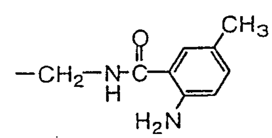
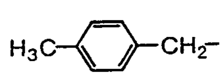
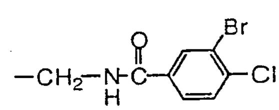
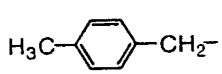
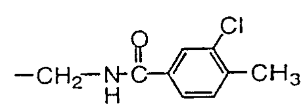
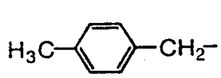
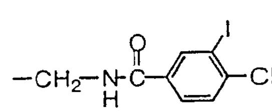
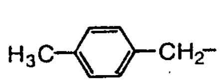
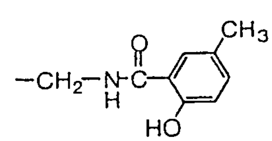
Compd. No.	R^1R^2>$-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1321		1	2	0	R	H	
1322		1	2	0	R	H	
1323		1	2	0	R	H	
1324		1	2	0	R	H	
1325		1	2	0	R	H	
1326		1	2	0	R	H	
1327		1	2	0	R	H	
1328		1	2	0	R	H	
1329		1	2	0	R	H	
1330		1	2	0	R	H	
1331		1	2	0	R	H	

Table 1.122

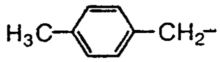
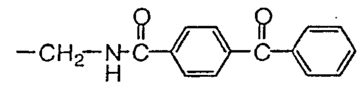
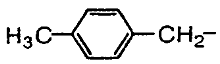
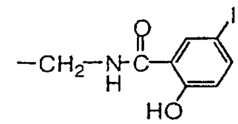
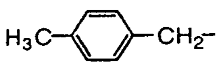
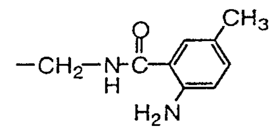
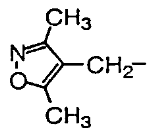
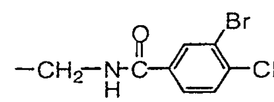
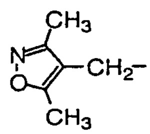
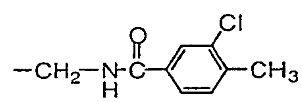
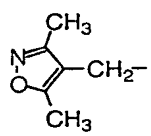
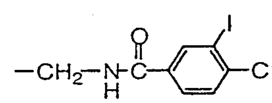
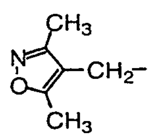
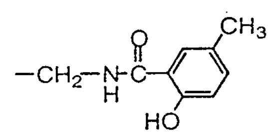
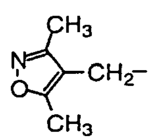
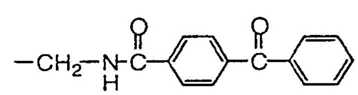
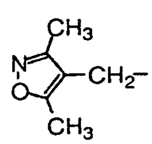
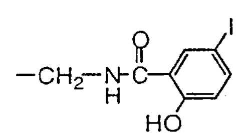
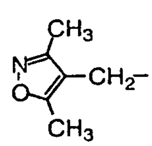
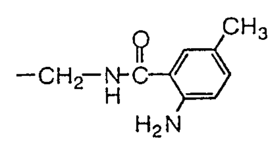
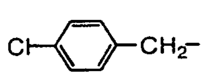
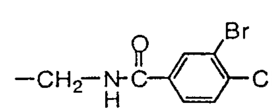
Compd. No.	$R^1R^2>$—$(CH_2)_j$—	k	m	n	chirality	R^3	—$(CH_2)_p$—$C(R^4)(R^5)$—$(CH_2)_q$—G—R^6
1332		1	2	0	R	H	
1333		1	2	0	R	H	
1334		1	2	0	R	H	
1335		1	2	0	R	H	
1336		1	2	0	R	H	
1337		1	2	0	R	H	
1338		1	2	0	R	H	
1339		1	2	0	R	H	
1340		1	2	0	R	H	
1341		1	2	0	R	H	
1342		2	2	1	-	H	

Table 1.123

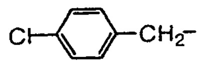
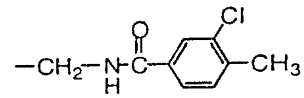
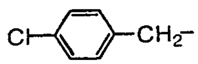
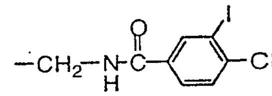
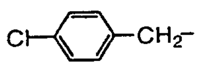
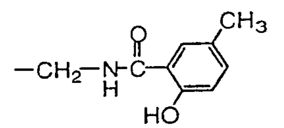
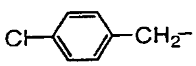
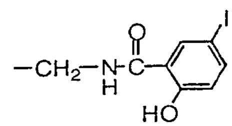
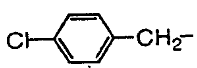
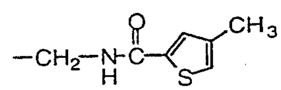
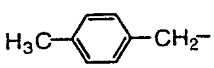
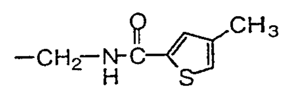
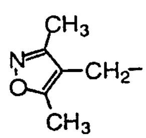
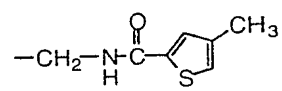
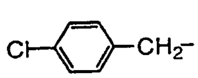
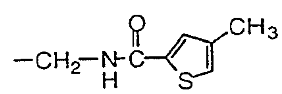
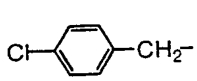
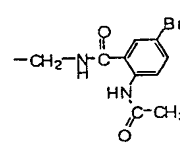
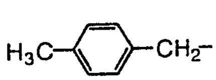
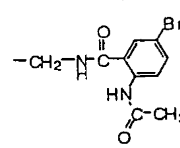
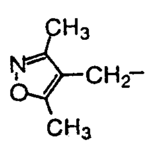
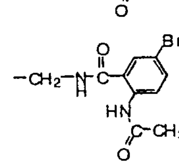
Compd. No.	$R^1(R^2)>-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1343		2	2	1	-	H	
1344		2	2	1	-	H	
1345		2	2	1	-	H	
1346		2	2	1	-	H	
1347		1	2	0	R	H	
1348		1	2	0	R	H	
1349		1	2	0	R	H	
1350		2	2	1	-	H	
1351		1	2	0	R	H	
1352		1	2	0	R	H	
1353		1	2	0	R	H	

Table 1.124

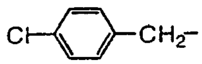
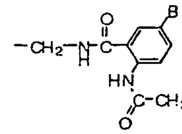
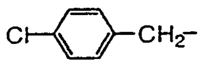
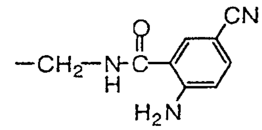
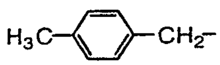
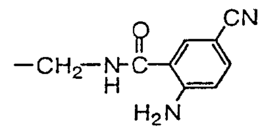
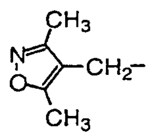
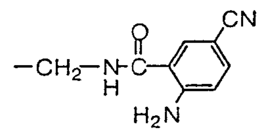
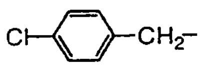
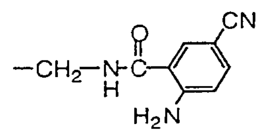
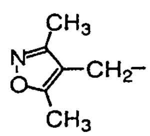
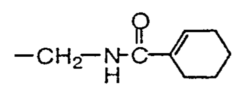
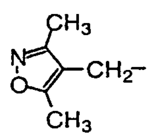
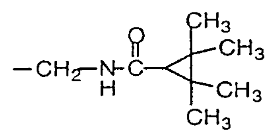
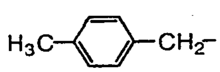
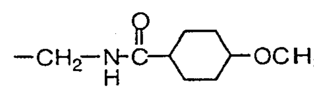
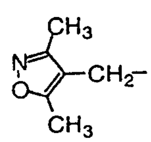
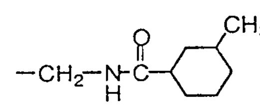
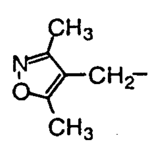
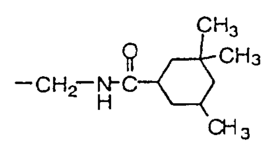
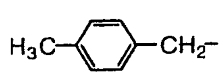
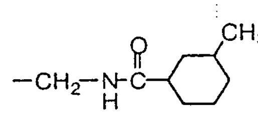
Compd. No.	R^1R^2>-$(CH_2)_j$-	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1354		2	2	1	-	H	
1355		1	2	0	R	H	
1356		1	2	0	R	H	
1357		1	2	0	R	H	
1358		2	2	1	-	H	
1359		1	2	0	R	H	
1360		1	2	0	R	H	
1361		1	2	0	R	H	
1362		1	2	0	R	H	
1363		1	2	0	R	H	
1364		1	2	0	R	H	

Table 1.125

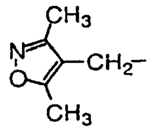
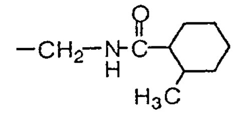
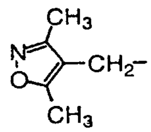
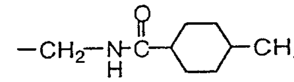
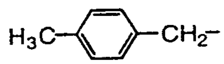
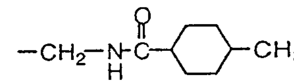
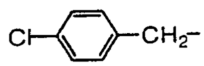
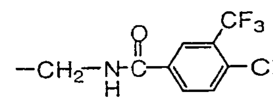
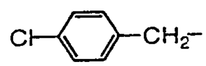
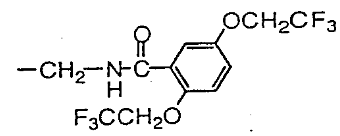
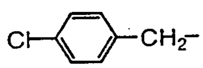
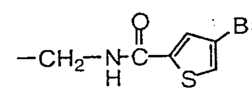
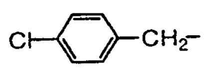
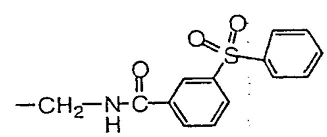
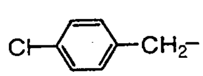
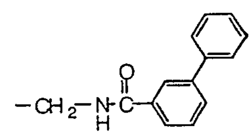
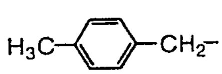
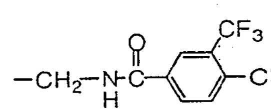
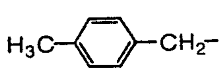
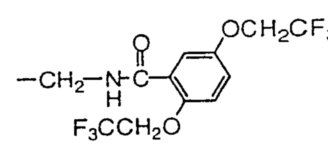
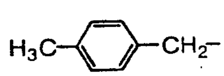
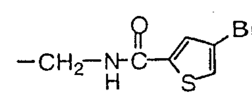
Compd. No.	R^1R^2>-$(CH_2)_j$-	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1365		1	2	0	R	H	
1366		1	2	0	R	H	
1367		1	2	0	R	H	
1368		1	2	0	R	H	
1369		1	2	0	R	H	
1370		1	2	0	R	H	
1371		1	2	0	R	H	
1372		1	2	0	R	H	
1373		1	2	0	R	H	
1374		1	2	0	R	H	
1375		1	2	0	R	H	

Table 1.126

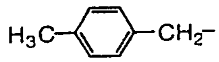
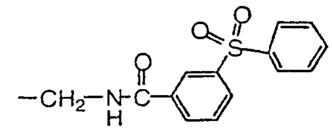
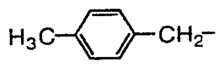
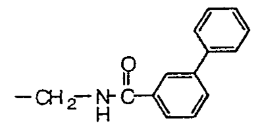
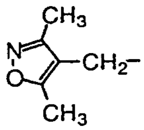
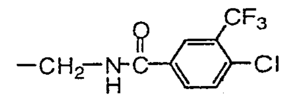
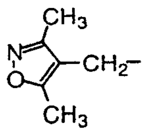
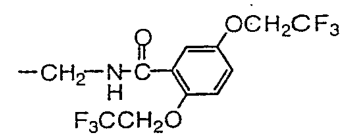
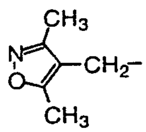
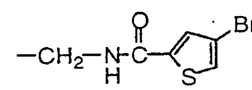
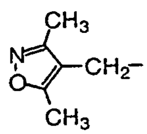
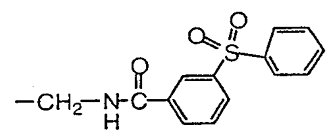
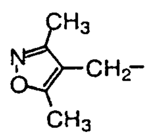
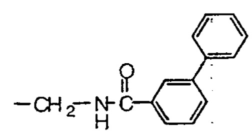
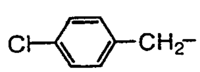
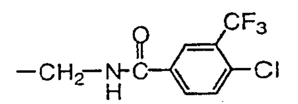
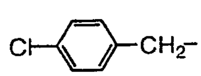
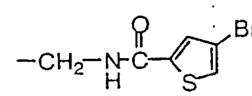
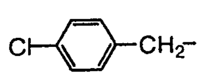
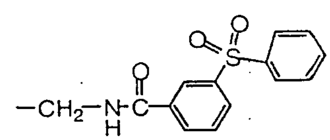
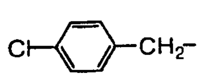
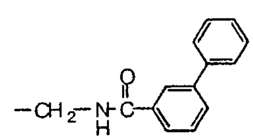
Compd. No.	R^1R^2>$-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1376		1	2	0	R	H	
1377		1	2	0	R	H	
1378		1	2	0	R	H	
1379		1	2	0	R	H	
1380		1	2	0	R	H	
1381		1	2	0	R	H	
1382		1	2	0	R	H	
1383		2	2	1	-	H	
1384		2	2	1	-	H	
1385		2	2	1	-	H	
1386		2	2	1	-	H	

Table 1.127

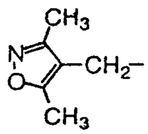
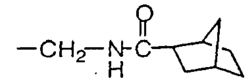
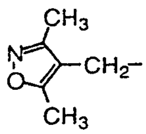
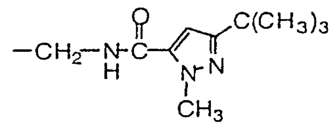
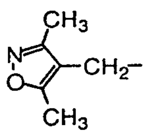
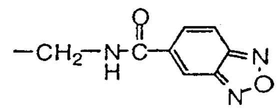
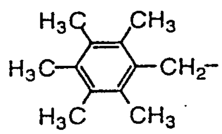
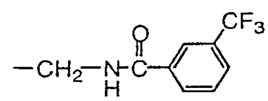
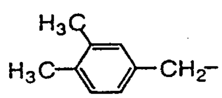
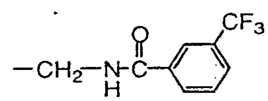
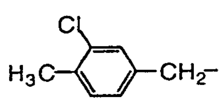
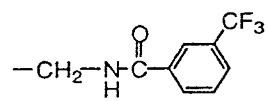
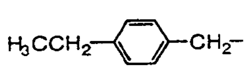
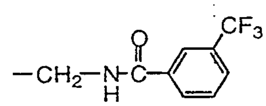
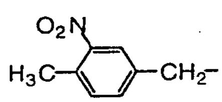
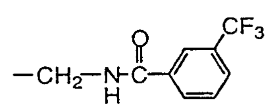
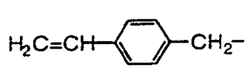
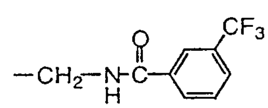
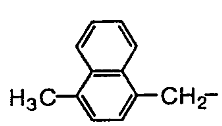
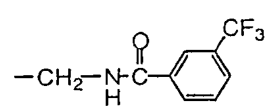
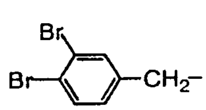
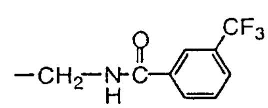
Compd. No.	R^1R^2>$-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1387		1	2	0	R	H	
1388		1	2	0	R	H	
1389		1	2	0	R	H	
1390		1	2	0	R	H	
1391		1	2	0	R	H	
1392		1	2	0	R	H	
1393		1	2	0	R	H	
1394		1	2	0	R	H	
1395		1	2	0	R	H	
1396		1	2	0	R	H	
1397		1	2	0	R	H	

Table 1.128

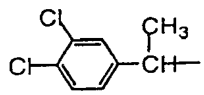
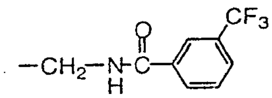
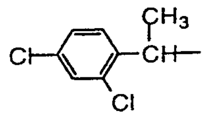
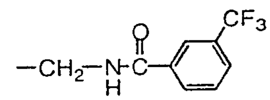
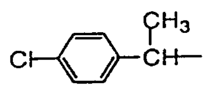
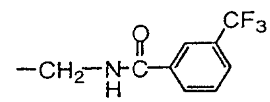
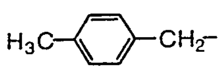
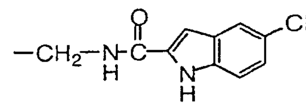
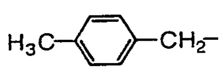
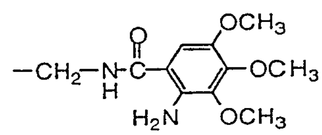
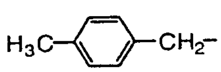
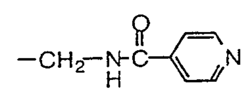
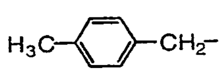
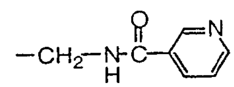
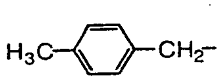
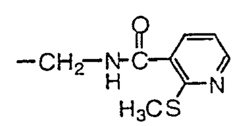
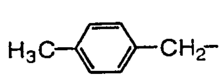
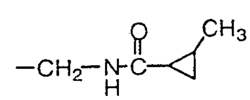
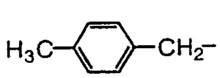
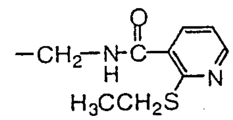
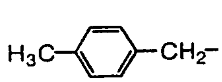
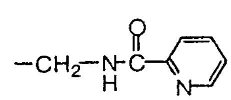
Compd. No.	$R^1R^2{>}\text{-}(CH_2)_j\text{-}$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1398		1	2	0	R	H	
1399		1	2	0	R	H	
1400		1	2	0	R	H	
1401		1	2	0	R	H	
1402		1	2	0	R	H	
1403		1	2	0	R	H	
1404		1	2	0	R	H	
1405		1	2	0	R	H	
1406		1	2	0	R	H	
1407		1	2	0	R	H	
1408		1	2	0	R	H	

Table 1.129

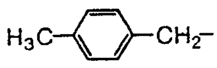
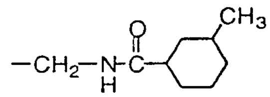
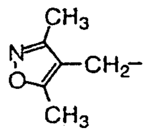
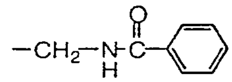
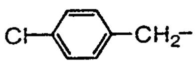
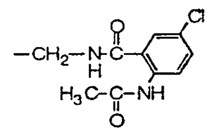
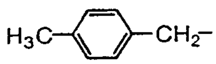
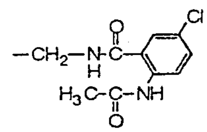
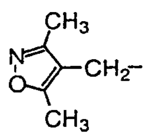
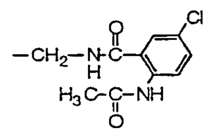
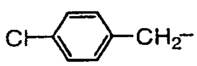
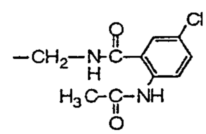
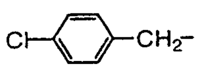
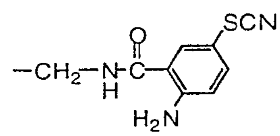
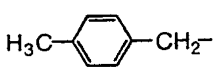
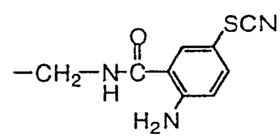
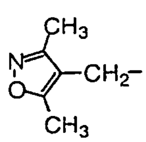
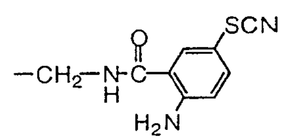
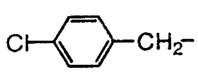
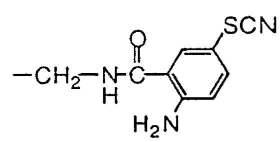
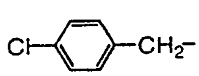
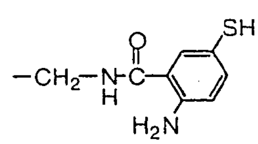
Compd. No.	$R^1R^2{>}(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1409		1	2	0	R	H	
1410		1	2	0	R	H	
1411		1	2	0	R	H	
1412		1	2	0	R	H	
1413		1	2	0	R	H	
1414		2	2	1	-	H	
1415		1	2	0	R	H	
1416		1	2	0	R	H	
1417		1	2	0	R	H	
1418		2	2	1	-	H	
1419		1	2	0	R	H	

Table 1.130

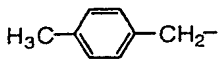
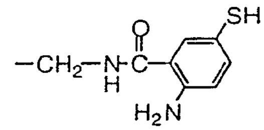
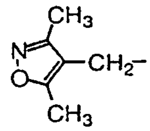
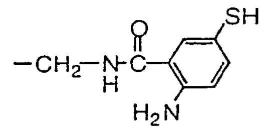
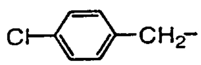
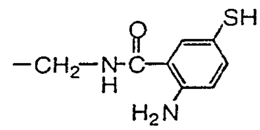
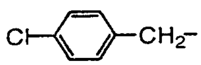
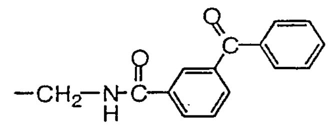
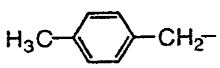
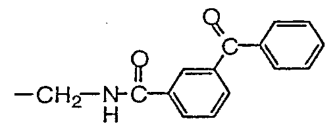
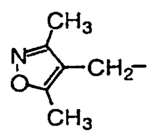
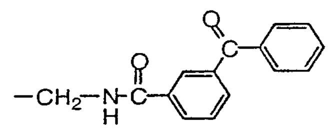
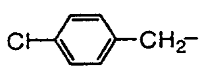
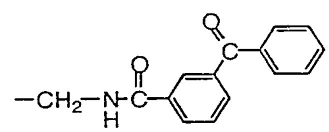
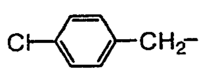
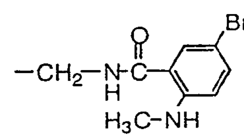
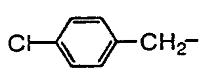
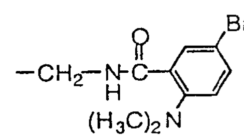
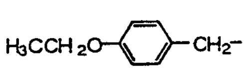
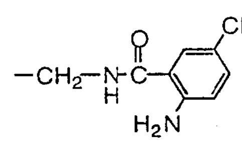
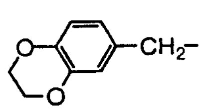
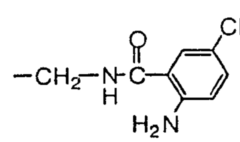
Compd. No.	R^1R^2>-$(CH_2)_j$–	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1420		1	2	0	R	H	
1421		1	2	0	R	H	
1422		2	2	1	-	H	
1423		1	2	0	R	H	
1424		1	2	0	R	H	
1425		1	2	0	R	H	
1426		2	2	1	-	H	
1427		2	2	1	-	H	
1428		2	2	1	-	H	
1429		2	2	1	-	H	
1430		2	2	1	-	H	

Table 1.131

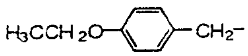
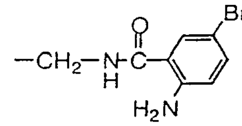
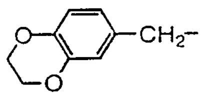
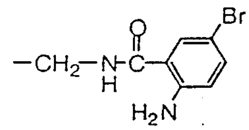
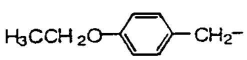
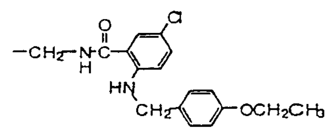
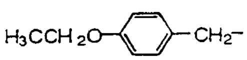
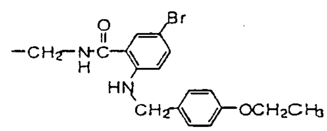
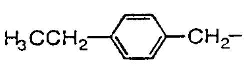
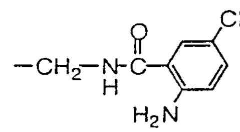
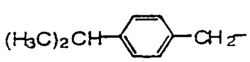
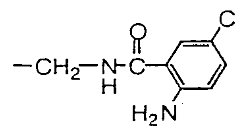
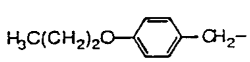
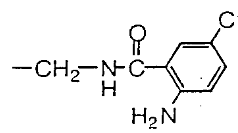
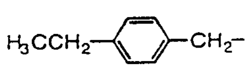
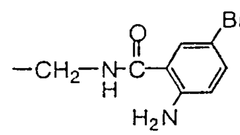
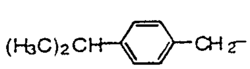
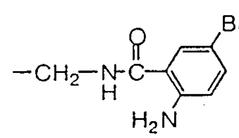
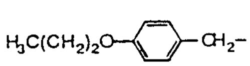
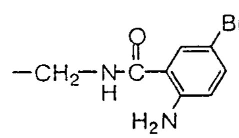
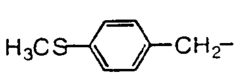
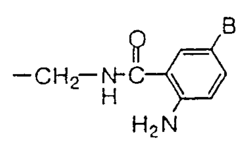
Compd. No.	R^1R^2>—$(CH_2)_j$—	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1431		2	2	1	-	H	
1432		2	2	1	-	H	
1433		2	2	1	-	H	
1434		2	2	1	-	H	
1435		2	2	1	-	H	
1436		2	2	1	-	H	
1437		2	2	1	-	H	
1438		2	2	1	-	H	
1439		2	2	1	-	H	
1440		2	2	1	-	H	
1441		2	2	1	-	H	

Table 1.132

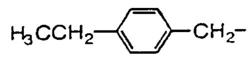
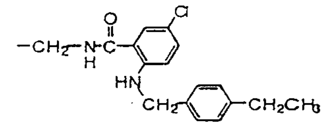
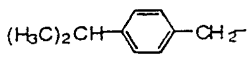
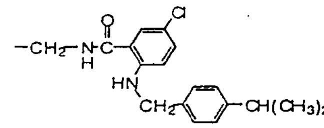
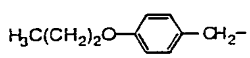
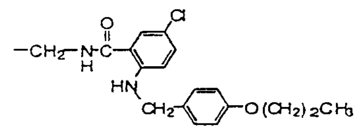
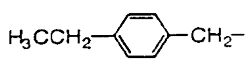
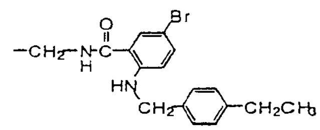
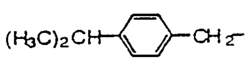
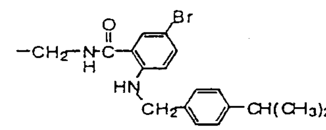
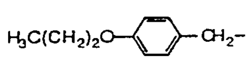
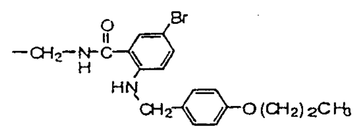
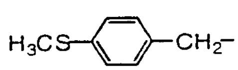
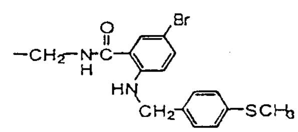
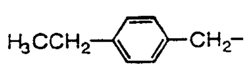
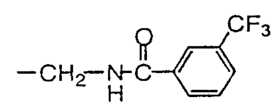
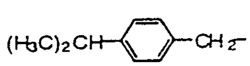
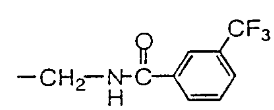
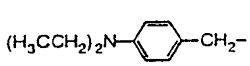
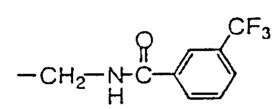
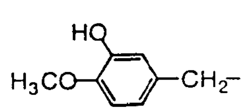
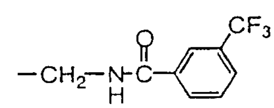
Compd. No.	$R^1R^2>$—$(CH_2)_j$—	k	m	n	chirality	R^3	—$(CH_2)_p$—$C(R^4)(R^5)$—$(CH_2)_q$—G—R^6
1442		2	2	1	-	H	
1443		2	2	1	-	H	
1444		2	2	1	-	H	
1445		2	2	1	-	H	
1446		2	2	1	-	H	
1447		2	2	1	-	H	
1448		2	2	1	-	H	
1449		2	2	1	-	H	
1450		2	2	1	-	H	
1451		2	2	1	-	H	
1452		2	2	1	-	H	

Table 1.133

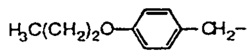
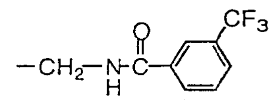
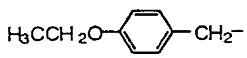
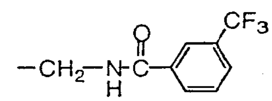
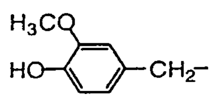
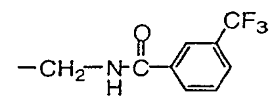
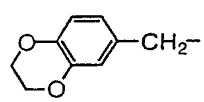
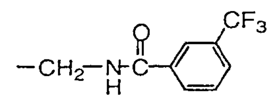
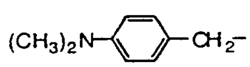
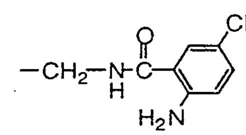
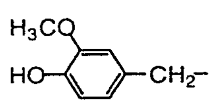
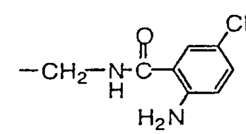
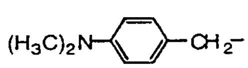
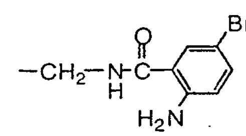
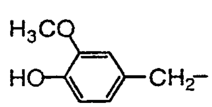
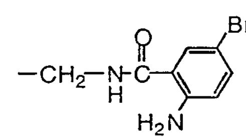
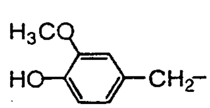
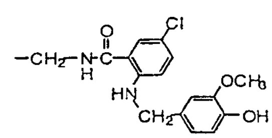
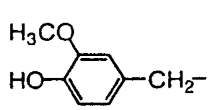
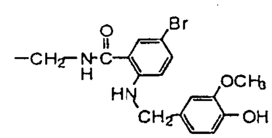
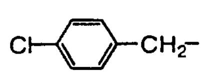
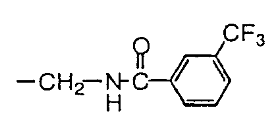
Compd. No.	$R^1R^2>(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1453		2	2	1	-	H	
1454		2	2	1	-	H	
1455		2	2	1	-	H	
1456		2	2	1	-	H	
1457		2	2	1	-	H	
1458		2	2	1	-	H	
1459		2	2	1	-	H	
1460		2	2	1	-	H	
1461		2	2	1	-	H	
1462		2	2	1	-	H	
1463		2	1	1	-	H	

Table 1.134

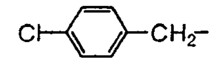
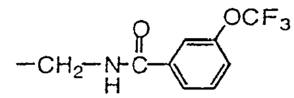
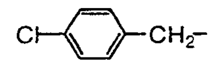
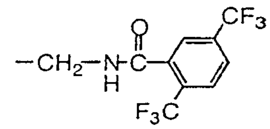
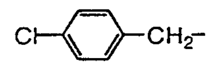
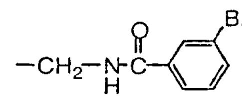
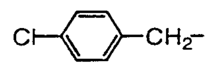
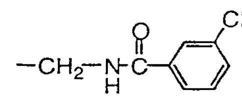
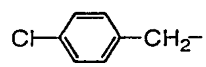
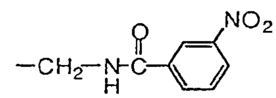
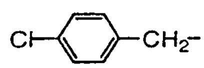
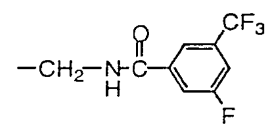
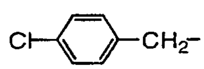
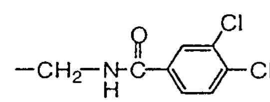
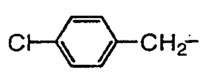
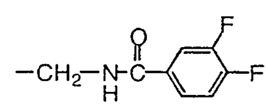
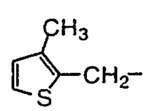
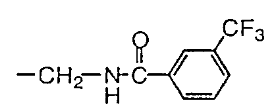
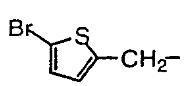
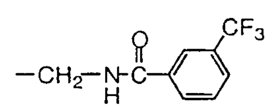
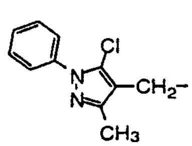
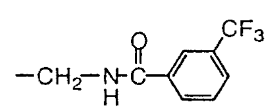
Compd. No.	R^1R^2>-$(CH_2)_j$–	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1464		2	1	1	-	H	
1465		2	1	1	-	H	
1466		2	1	1	-	H	
1467		2	1	1	-	H	
1468		2	1	1	-	H	
1469		2	1	1	-	H	
1470		2	1	1	-	H	
1471		2	1	1	-	H	
1472		1	2	0	R	H	
1473		1	2	0	R	H	
1474		1	2	0	R	H	

Table 1.135

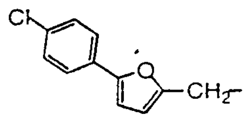
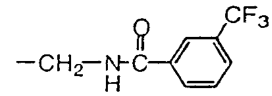
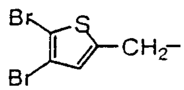
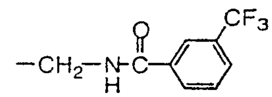
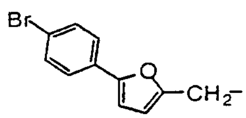
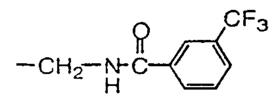
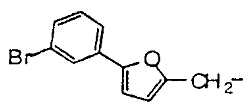
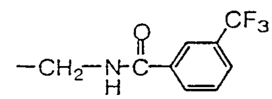
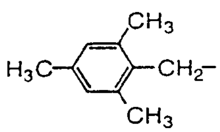
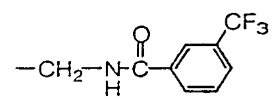
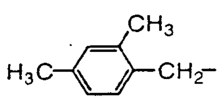
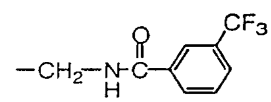
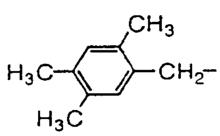
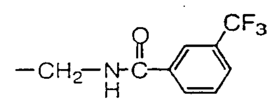
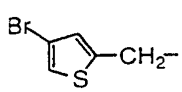
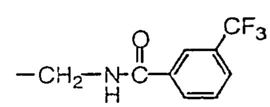
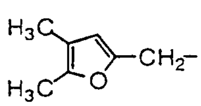
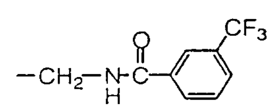
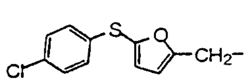
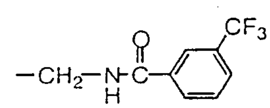
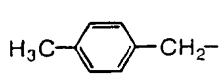
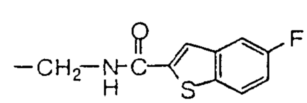
Compd. No.	$R^1R^2>-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1475		1	2	0	R	H	
1476		1	2	0	R	H	
1477		1	2	0	R	H	
1478		1	2	0	R	H	
1479		1	2	0	R	H	
1480		1	2	0	R	H	
1481		1	2	0	R	H	
1482		1	2	0	R	H	
1483		1	2	0	R	H	
1484		1	2	0	R	H	
1485		1	2	0	R	H	

Table 1.136

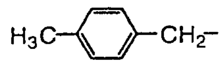
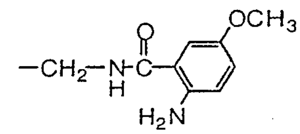
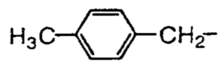
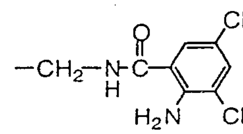
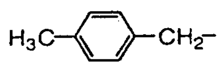
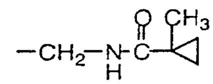
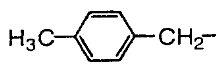
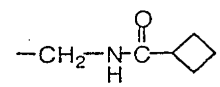
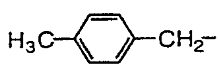
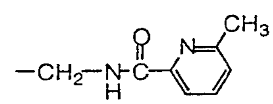
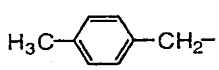
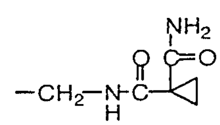
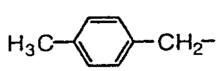
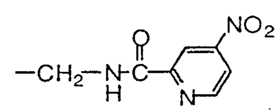
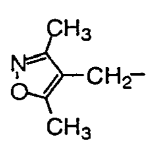
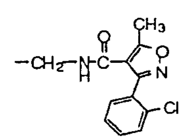
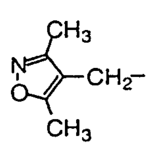
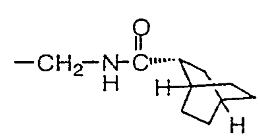
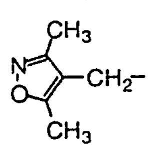
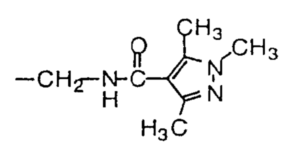
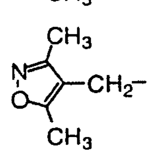
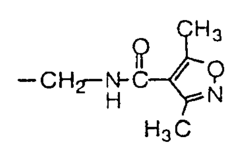
Compd. No.	$R^1R^2>(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1486		1	2	0	R	H	
1487		1	2	0	R	H	
1488		1	2	0	R	H	
1489		1	2	0	R	H	
1490		1	2	0	R	H	
1491		1	2	0	R	H	
1492		1	2	0	R	H	
1493		1	2	0	R	H	
1494		1	2	0	R	H	
1495		1	2	0	R	H	
1496		1	2	0	R	H	

Table 1.137

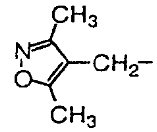
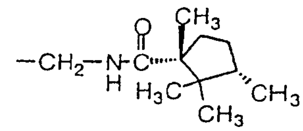
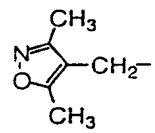
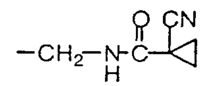
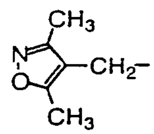
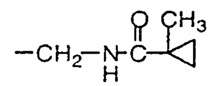
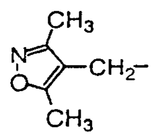
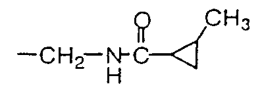
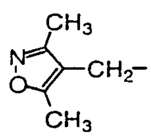
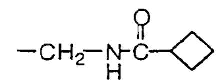
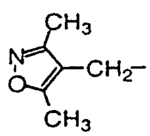
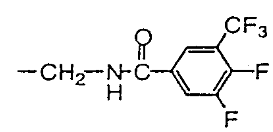
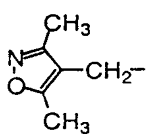
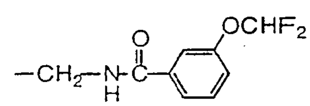
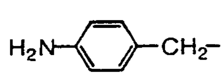
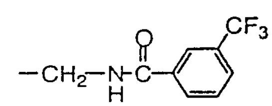
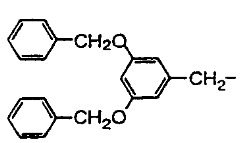
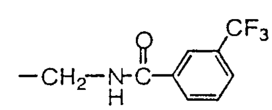
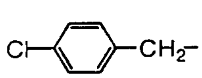
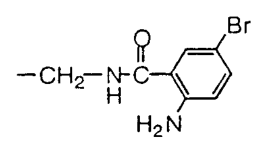
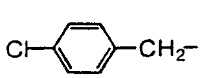
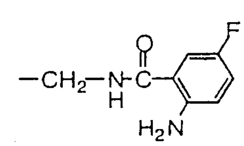
Compd. No.	$R^1R^2CH-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1497		1	2	0	R	H	
1498		1	2	0	R	H	
1499		1	2	0	R	H	
1500		1	2	0	R	H	
1501		1	2	0	R	H	
1502		1	2	0	R	H	
1503		1	2	0	R	H	
1504		1	2	0	R	H	
1505		1	2	0	R	H	
1506		2	1	1	-	H	
1507		2	1	1	-	H	

Table 1.138

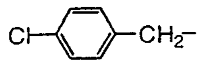
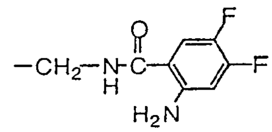
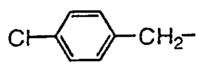
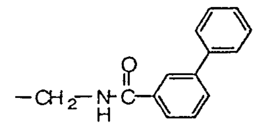
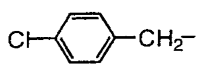
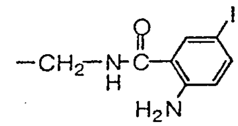
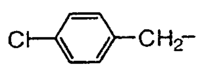
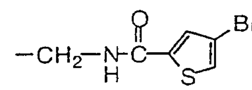
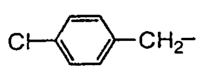
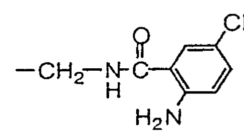
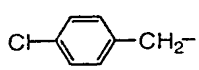
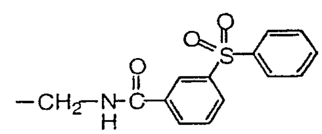
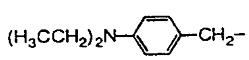
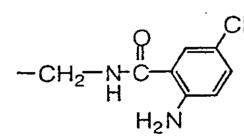
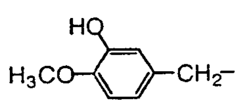
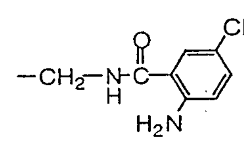
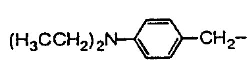
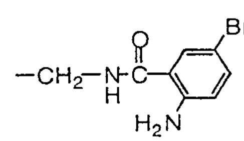
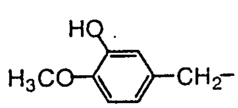
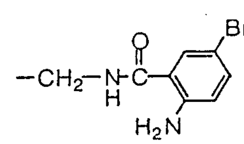
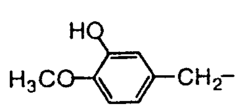
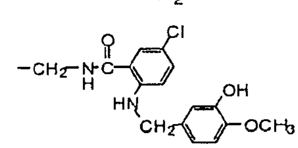
Compd. No.	$R^1R^2>$—$(CH_2)_j$—	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1508		2	1	1	-	H	
1509		2	1	1	-	H	
1510		2	1	1	-	H	
1511		2	1	1	-	H	
1512		2	1	1	-	H	
1513		2	1	1	-	H	
1514		2	2	1	-	H	
1515		2	2	1	-	H	
1516		2	2	1	-	H	
1517		2	2	1	-	H	
1518		2	2	1	-	H	

Table 1.139

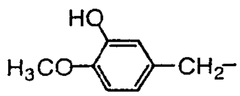
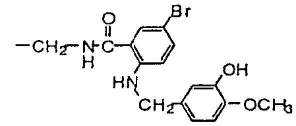
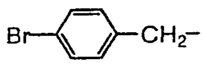
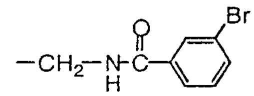
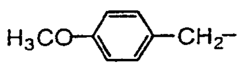
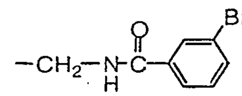
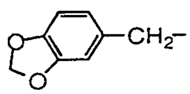
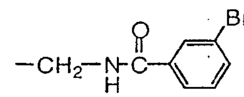
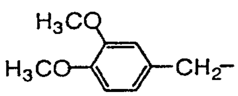
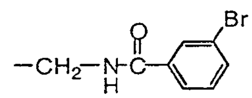
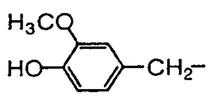
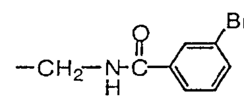
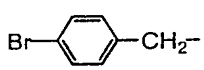
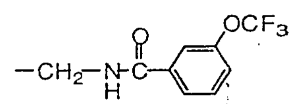
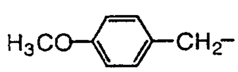
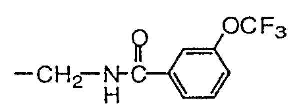
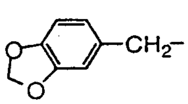
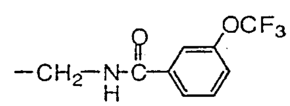
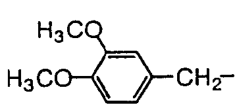
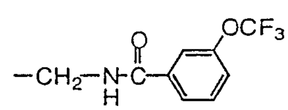
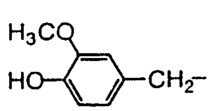
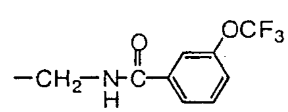
Compd. No.	$R^1R^2>$—$(CH_2)_j$—	k	m	n	chirality	R^3	—$(CH_2)_p$—$C(R^4)(R^5)$—$(CH_2)_q$—G—R^6
1519		2	2	1	-	H	
1520		1	2	0	R	H	
1521		1	2	0	R	H	
1522		1	2	0	R	H	
1523		1	2	0	R	H	
1524		1	2	0	R	H	
1525		1	2	0	R	H	
1526		1	2	0	R	H	
1527		1	2	0	R	H	
1528		1	2	0	R	H	
1529		1	2	0	R	H	

Table 1.140

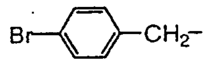
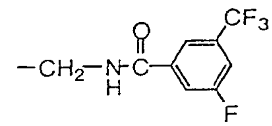
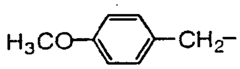
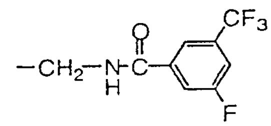
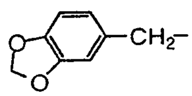
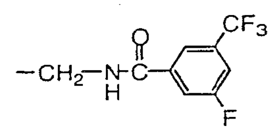
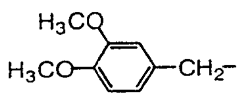
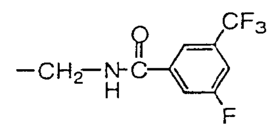
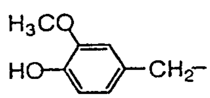
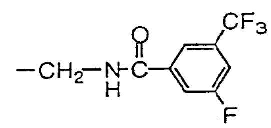
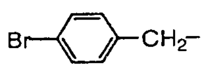
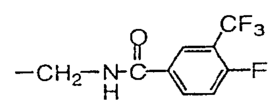
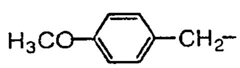
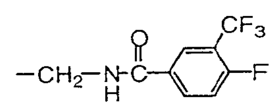
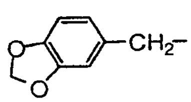
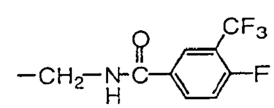
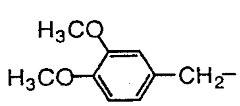
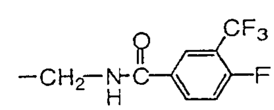
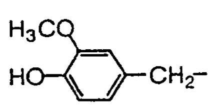
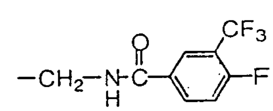
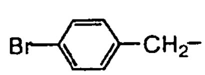
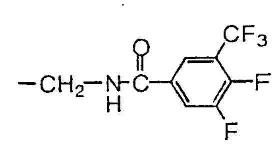
Compd. No.	R^1R^2>$-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1530		1	2	0	R	H	
1531		1	2	0	R	H	
1532		1	2	0	R	H	
1533		1	2	0	R	H	
1534		1	2	0	R	H	
1535		1	2	0	R	H	
1536		1	2	0	R	H	
1537		1	2	0	R	H	
1538		1	2	0	R	H	
1539		1	2	0	R	H	
1540		1	2	0	R	H	

Table 1.141

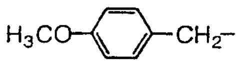
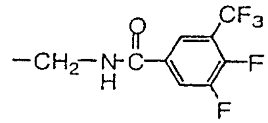
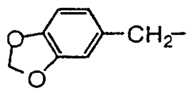
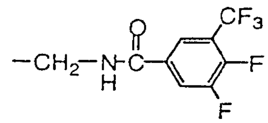
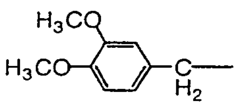
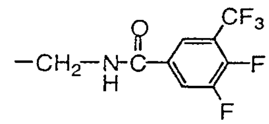
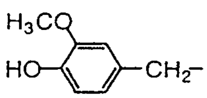
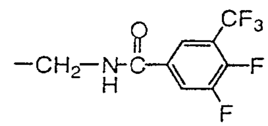
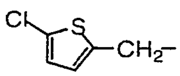
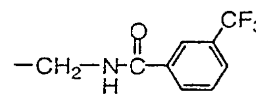
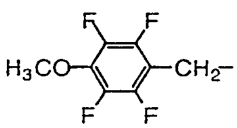
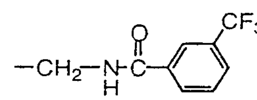
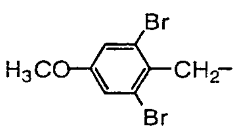
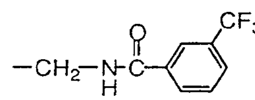
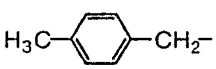
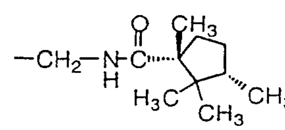
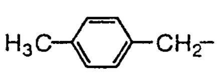
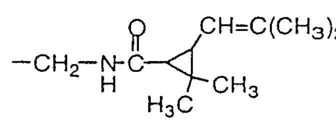
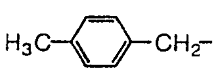
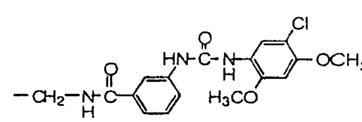
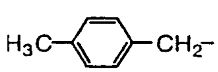
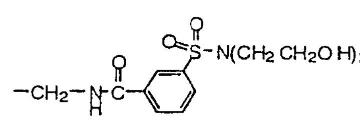
Compd. No.	R^1R^2>-$(CH_2)_j$-	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1541		1	2	0	R	H	
1542		1	2	0	R	H	
1543		1	2	0	R	H	
1544		1	2	0	R	H	
1545		1	2	0	R	H	
1546		1	2	0	R	H	
1547		1	2	0	R	H	
1548		1	2	0	R	H	
1549		1	2	0	R	H	
1550		1	2	0	R	H	
1551		1	2	0	R	H	

Table 1.142

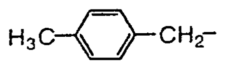
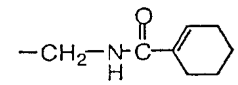
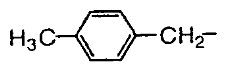
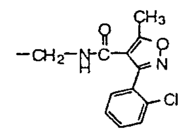
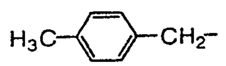
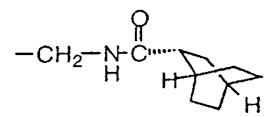
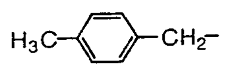
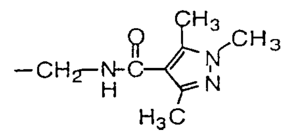
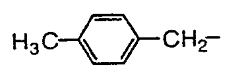
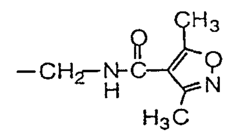
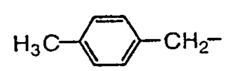
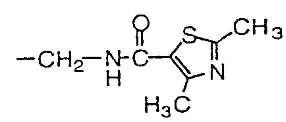
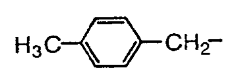
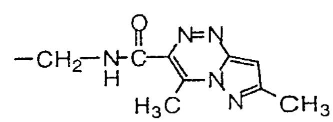
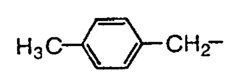
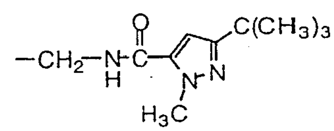
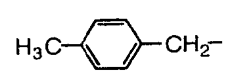
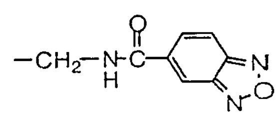
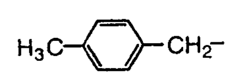
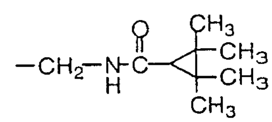
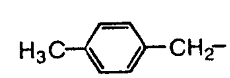
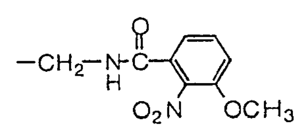
Compd. No.	$R^1R^2>-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1552		1	2	0	R	H	
1553		1	2	0	R	H	
1554		1	2	0	R	H	
1555		1	2	0	R	H	
1556		1	2	0	R	H	
1557		1	2	0	R	H	
1558		1	2	0	R	H	
1559		1	2	0	R	H	
1560		1	2	0	R	H	
1561		1	2	0	R	H	
1562		1	2	0	R	H	

Table 1.143

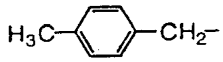
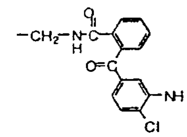
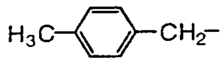
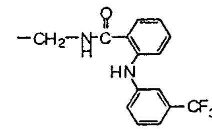
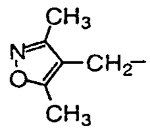
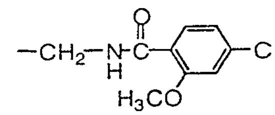
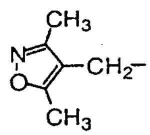
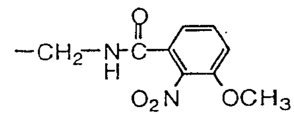
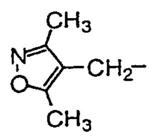
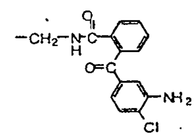
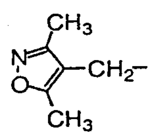
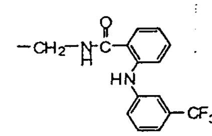
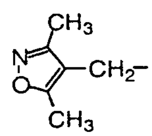
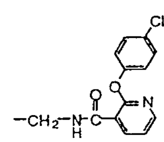
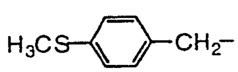
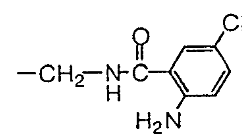
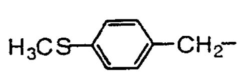
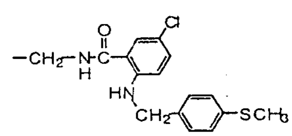
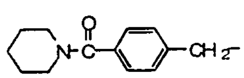
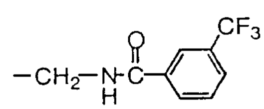
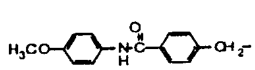
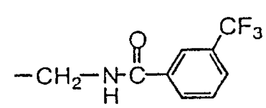
Compd. No.	$R^1R^2>$–$(CH_2)_j$–	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1563		1	2	0	R	H	
1564		1	2	0	R	H	
1565		1	2	0	R	H	
1566		1	2	0	R	H	
1567		1	2	0	R	H	
1568		1	2	0	R	H	
1569		1	2	0	R	H	
1570		2	2	1	-	H	
1571		2	2	1	-	H	
1572		2	2	1	-	H	
1573		2	2	1	-	H	

Table 1.144

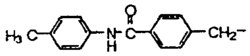
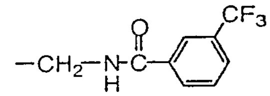
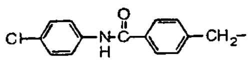
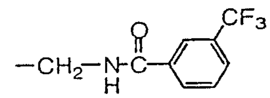
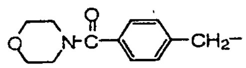
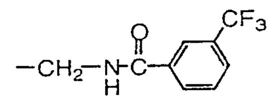
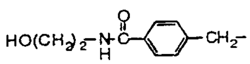
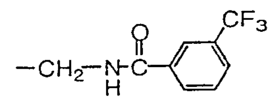
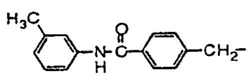
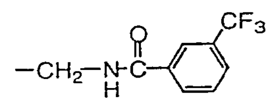
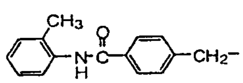
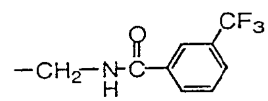
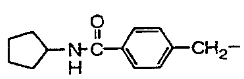
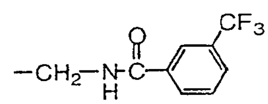
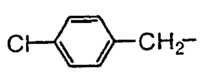
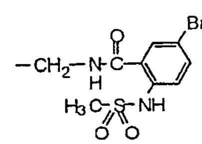
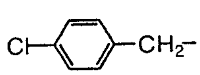
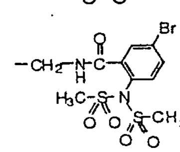
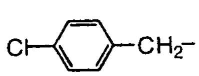
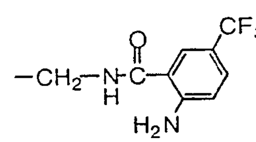
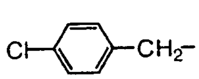
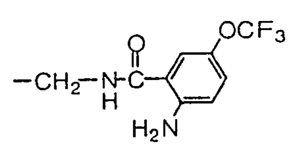
Compd. No.	$R^1R^2>$—$(CH_2)_j$—	k	m	n	chirality	R^3	—$(CH_2)_p$—$C(R^4)(R^5)$—$(CH_2)_q$—G—R^6
1574		2	2	1	-	H	
1575		2	2	1	-	H	
1576		2	2	1	-	H	
1577		2	2	1	-	H	
1578		2	2	1	-	H	
1579		2	2	1	-	H	
1580		2	2	1	-	H	
1581		2	2	1	-	H	
1582		2	2	1	-	H	
1583		1	2	0	R	H	
1584		1	2	0	R	H	

Table 1.145

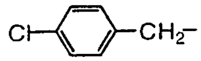
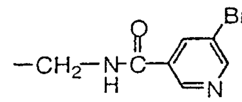
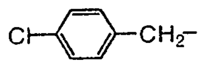
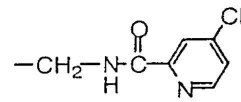
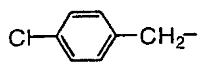
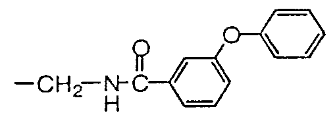
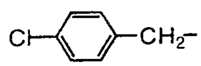
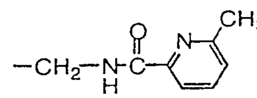
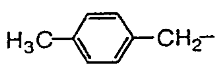
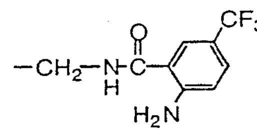
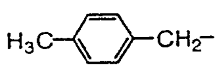
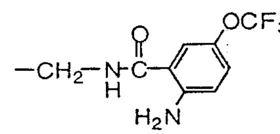
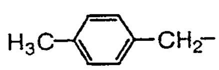
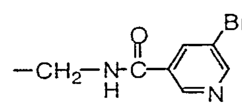
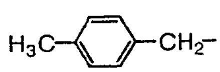
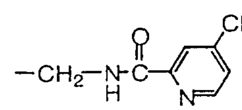
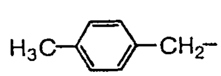
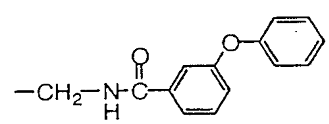
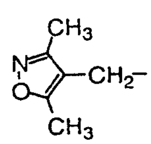
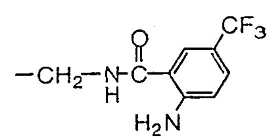
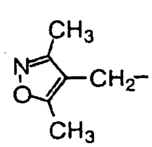
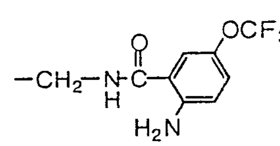
Compd. No.	$\begin{matrix}R^1\\R^2\end{matrix}\!>\!(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{\vert}}-(CH_2)_q-G-R^6$
1585		1	2	0	R	H	
1586		1	2	0	R	H	
1587		1	2	0	R	H	
1588		1	2	0	R	H	
1589		1	2	0	R	H	
1590		1	2	0	R	H	
1591		1	2	0	R	H	
1592		1	2	0	R	H	
1593		1	2	0	R	H	
1594		1	2	0	R	H	
1595		1	2	0	R	H	

Table 1.146

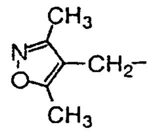
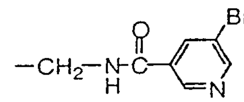
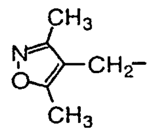
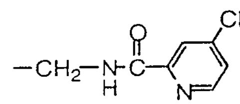
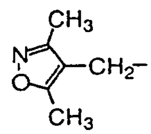
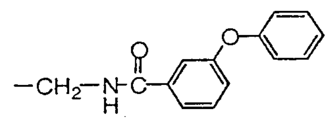
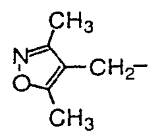
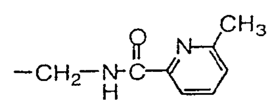
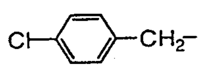
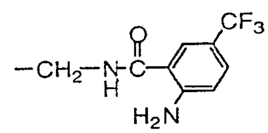
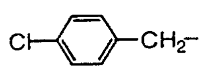
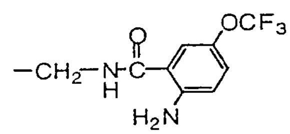
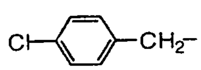
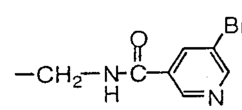
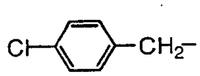
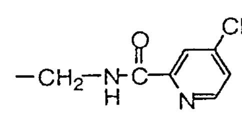
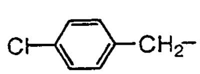
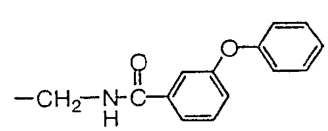
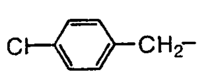
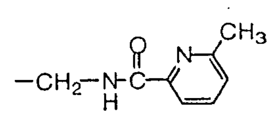
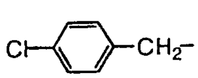
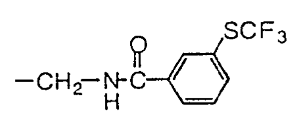
Compd. No.	$R^1R^2>(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1596		1	2	0	R	H	
1597		1	2	0	R	H	
1598		1	2	0	R	H	
1599		1	2	0	R	H	
1600		2	2	1	-	H	
1601		2	2	1	-	H	
1602		2	2	1	-	H	
1603		2	2	1	-	H	
1604		2	2	1	-	H	
1605		2	2	1	-	H	
1606		1	2	0	R	H	

Table 1.147

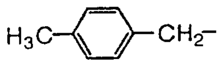
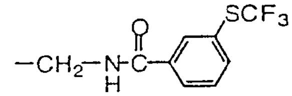
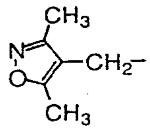
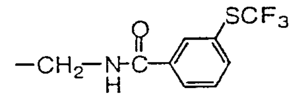
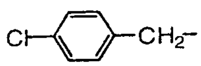
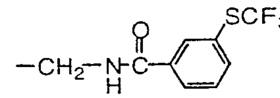
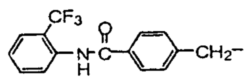
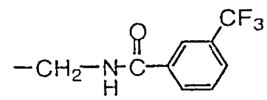
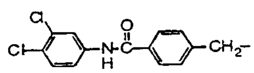
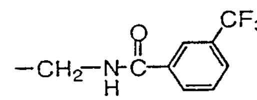
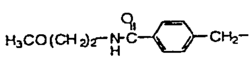
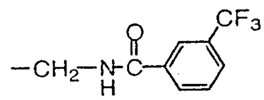
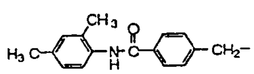
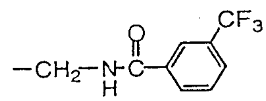
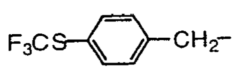
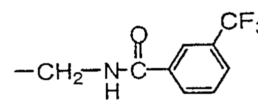
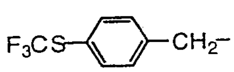
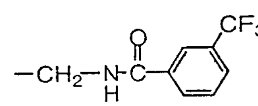
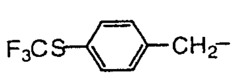
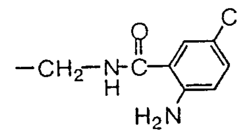
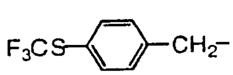
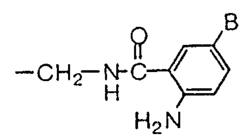
Compd. No.	$R^1R^2>$–$(CH_2)_j$–	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1607		1	2	0	R	H	
1608		1	2	0	R	H	
1609		2	2	1	-	H	
1610		2	2	1	-	H	
1611		2	2	1	-	H	
1612		2	2	1	-	H	
1613		2	2	1	-	H	
1614		1	2	0	R	H	
1615		2	2	1	-	H	
1616		2	2	1	-	H	
1617		2	2	1	-	H	

Table 1.148

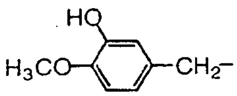
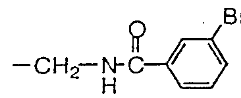
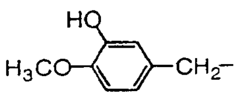
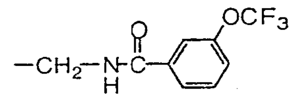
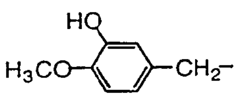
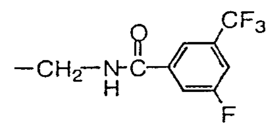
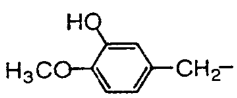
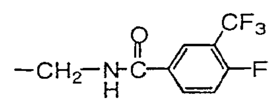
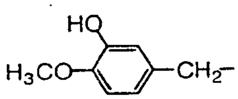
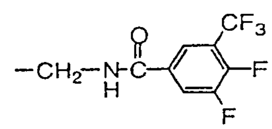
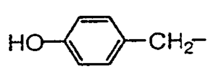
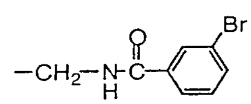
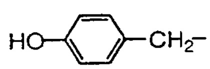
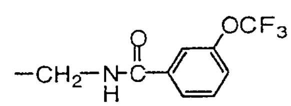
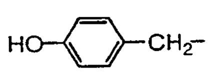
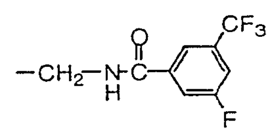
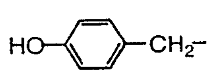
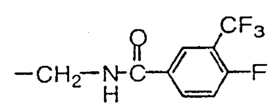
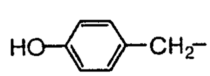
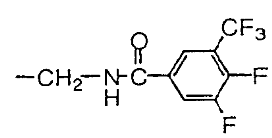
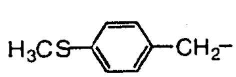
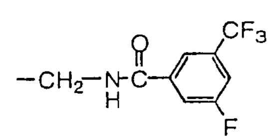
Compd. No.	$R^1R^2>(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-\overset{R^4}{\underset{R^5}{C}}-(CH_2)_q-G-R^6$
1618		1	2	0	R	H	
1619		1	2	0	R	H	
1620		1	2	0	R	H	
1621		1	2	0	R	H	
1622		1	2	0	R	H	
1623		1	2	0	R	H	
1624		1	2	0	R	H	
1625		1	2	0	R	H	
1626		1	2	0	R	H	
1627		1	2	0	R	H	
1628		1	2	0	R	H	

Table 1.149

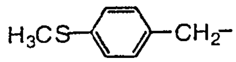
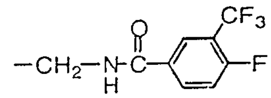
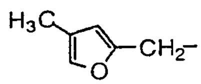
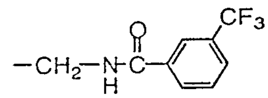
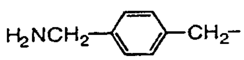
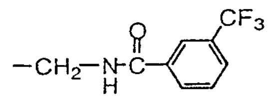
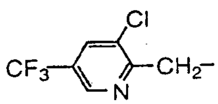
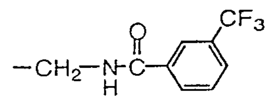
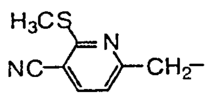
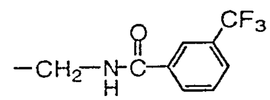
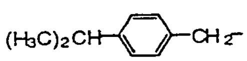
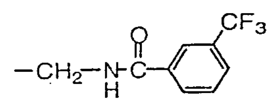
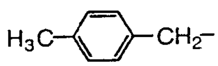
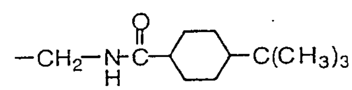
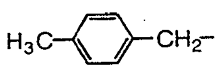
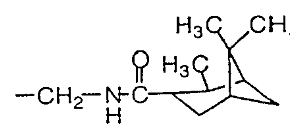
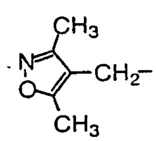
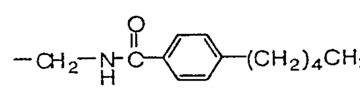
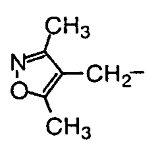
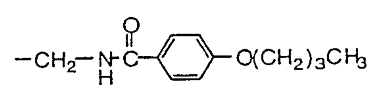
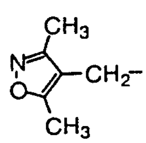
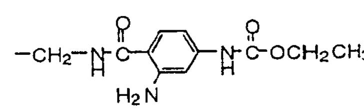
Compd. No.	$R^1R^2>$–$(CH_2)_j$–	k	m	n	chirality	R^3	–$(CH_2)_p$–$C(R^4)(R^5)$–$(CH_2)_q$–G–R^6
1629		1	2	0	R	H	
1630		1	2	0	R	H	
1631		1	2	0	R	H	
1632		1	2	0	R	H	
1633		1	2	0	R	H	
1634		1	2	0	R	H	
1635		1	2	0	R	H	
1636		1	2	0	R	H	
1637		1	2	0	R	H	
1638		1	2	0	R	H	
1639		1	2	0	R	H	

Table 1.150

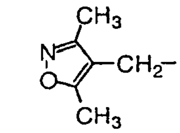
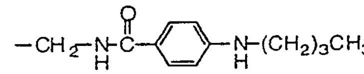
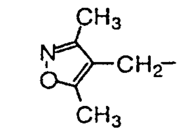
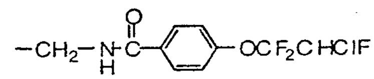
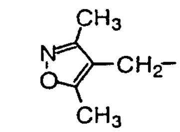
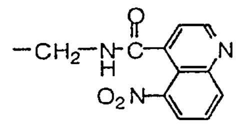
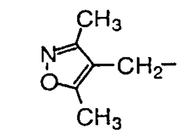
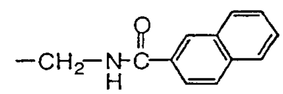
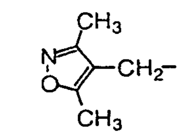
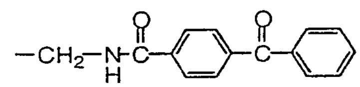
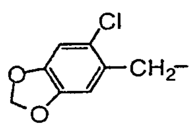
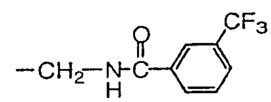
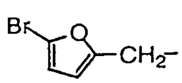
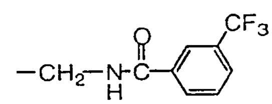
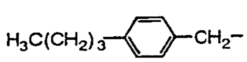
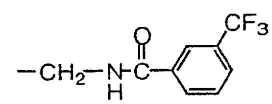
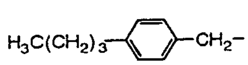
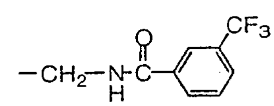
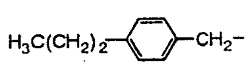
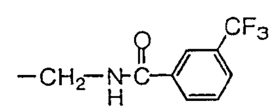
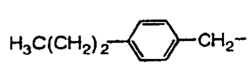
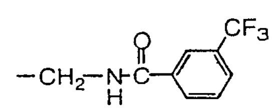
Compd. No.	$R^1R^2>-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1640		1	2	0	R	H	
1641		1	2	0	R	H	
1642		1	2	0	R	H	
1643		1	2	0	R	H	
1644		1	2	0	R	H	
1645		1	2	0	R	H	
1646		1	2	0	R	H	
1647		2	2	1	-	H	
1648		1	2	0	R	H	
1649		2	2	1	-	H	
1650		1	2	0	R	H	

Table 1.151

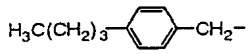
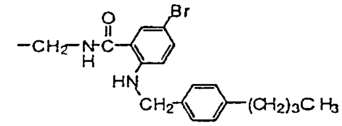
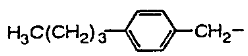
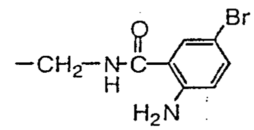
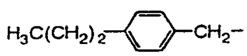
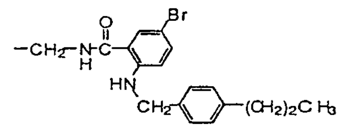
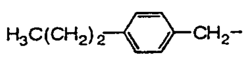
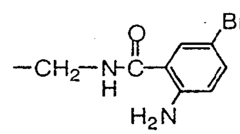
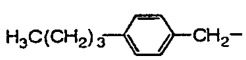
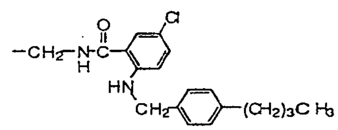
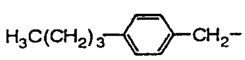
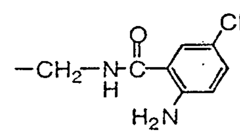
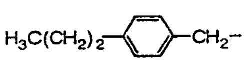
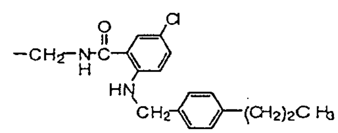
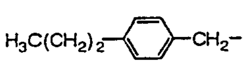
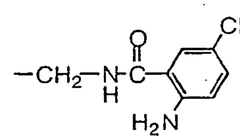
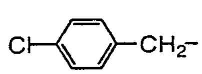
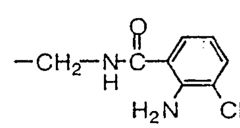
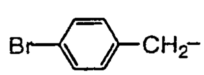
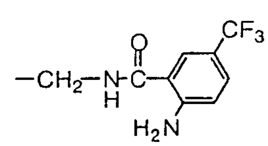
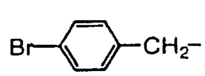
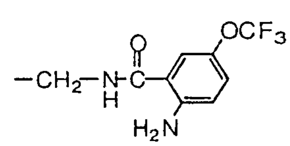
Compd. No.	$R^1R^2>(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1651		2	2	1	-	H	
1652		2	2	1	-	H	
1653		2	2	1	-	H	
1654		2	2	1	-	H	
1655		2	2	1	-	H	
1656		2	2	1	-	H	
1657		2	2	1	-	H	
1658		2	2	1	-	H	
1659		2	2	1	-	H	
1660		1	2	0	R	H	
1661		1	2	0	R	H	

Table 1.152

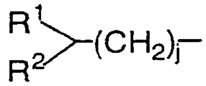
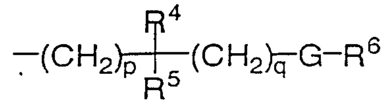
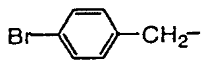
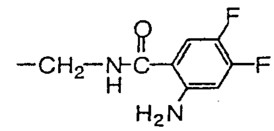
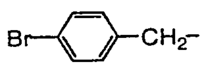
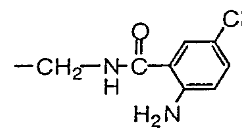
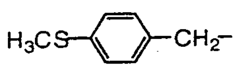
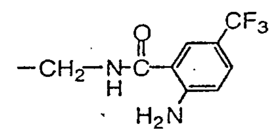
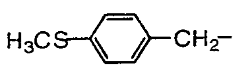
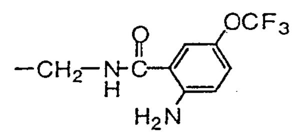
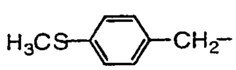
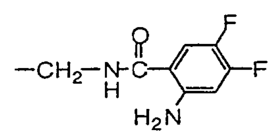
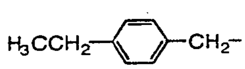
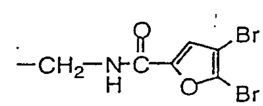
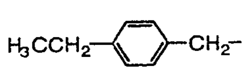
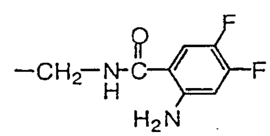
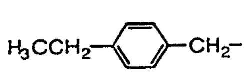
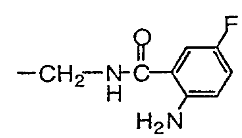
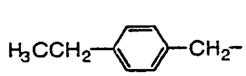
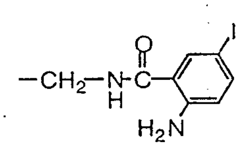
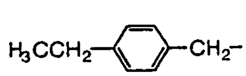
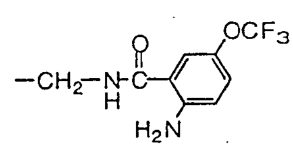
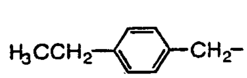
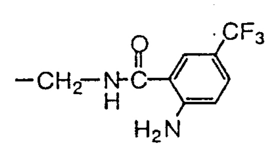
Compd. No.		k	m	n	chirality	R^3	
1662		1	2	0	R	H	
1663		1	2	0	R	H	
1664		2	2	1	-	H	
1665		2	2	1	-	H	
1666		2	2	1	-	H	
1667		2	2	1	-	H	
1668		2	2	1	-	H	
1669		2	2	1	-	H	
1670		2	2	1	-	H	
1671		2	2	1	-	H	
1672		2	2	1	-	H	

Table 1.153

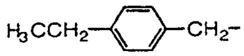
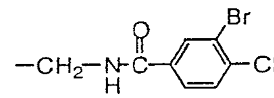
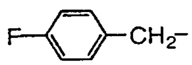
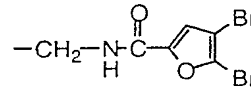
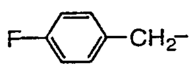
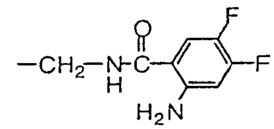
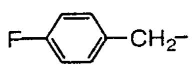
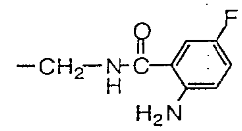
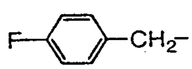
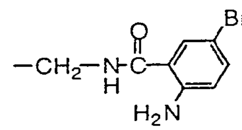
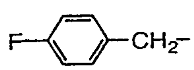
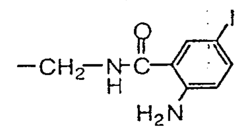
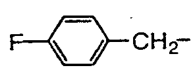
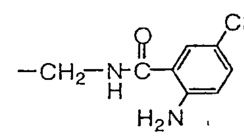
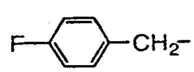
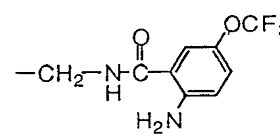
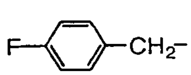
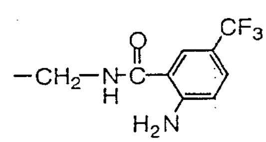
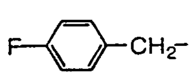
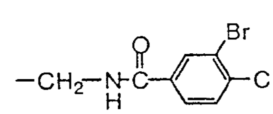
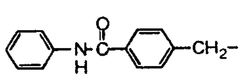
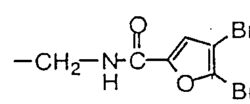
Compd. No.	R^1R^2 >–$(CH_2)_j$–	k	m	n	chirality	R^3	–$(CH_2)_p$–$C(R^4)(R^5)$–$(CH_2)_q$–G–R^6
1673		2	2	1	-	H	
1674		2	2	1	-	H	
1675		2	2	1	-	H	
1676		2	2	1	-	H	
1677		2	2	1	-	H	
1678		2	2	1	-	H	
1679		2	2	1	-	H	
1680		2	2	1	-	H	
1681		2	2	1	-	H	
1682		2	2	1	-	H	
1683		2	2	1	-	H	

Table 1.154

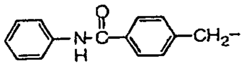
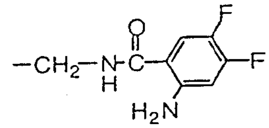
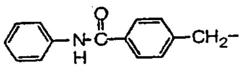
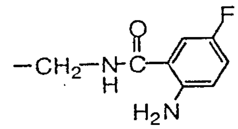
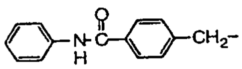
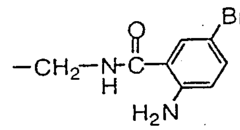
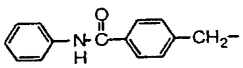
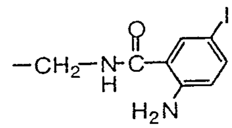
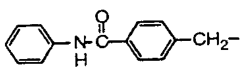
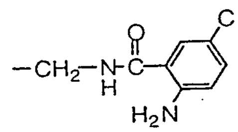
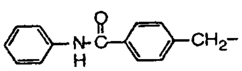
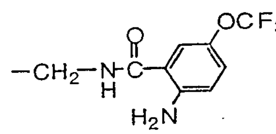
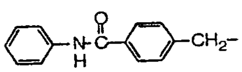
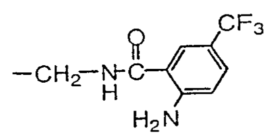
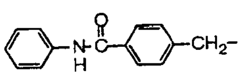
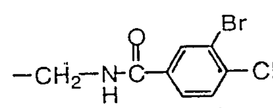
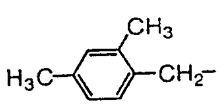
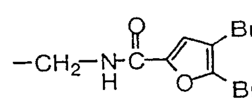
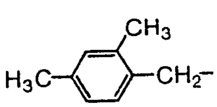
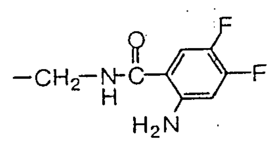
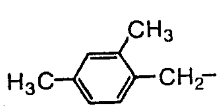
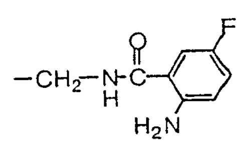
Compd. No.	$R^1R^2>-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1684		2	2	1	-	H	
1685		2	2	1	-	H	
1686		2	2	1	-	H	
1687		2	2	1	-	H	
1688		2	2	1	-	H	
1689		2	2	1	-	H	
1690		2	2	1	-	H	
1691		2	2	1	-	H	
1692		1	2	0	R	H	
1693		1	2	0	R	H	
1694		1	2	0	R	H	

Table 1.155

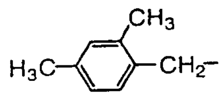
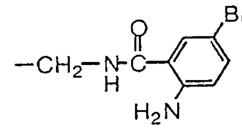
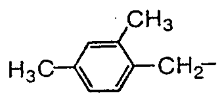
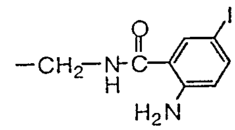
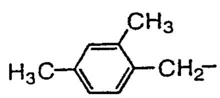
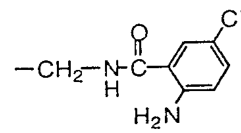
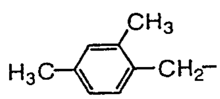
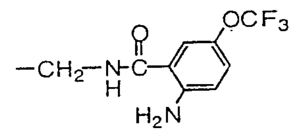
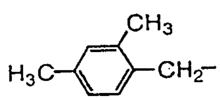
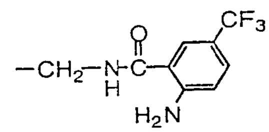
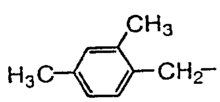
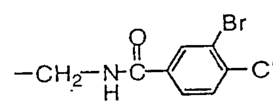
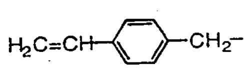
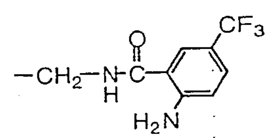
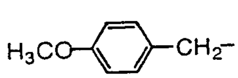
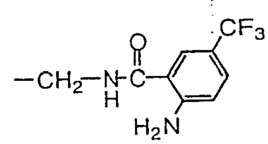
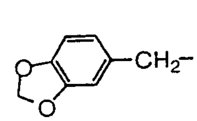
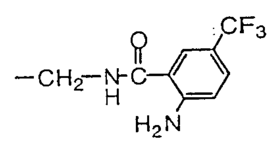
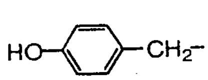
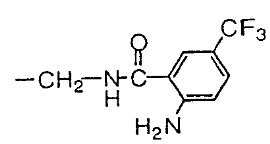
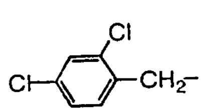
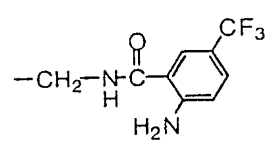
Compd. No.	$R^1R^2>$—$(CH_2)_j$—	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1695		1	2	0	R	H	
1696		1	2	0	R	H	
1697		1	2	0	R	H	
1698		1	2	0	R	H	
1699		1	2	0	R	H	
1700		1	2	0	R	H	
1701		1	2	0	R	H	
1702		1	2	0	R	H	
1703		1	2	0	R	H	
1704		1	2	0	R	H	
1705		1	2	0	R	H	

Table 1.156

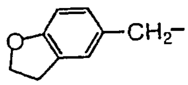
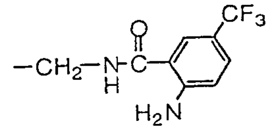
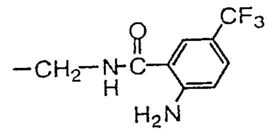
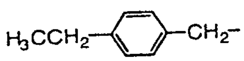
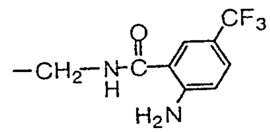
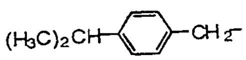
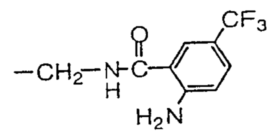
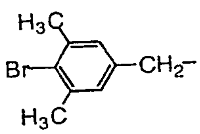
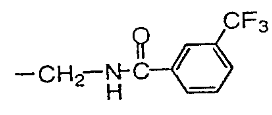
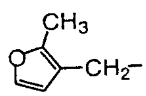
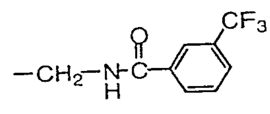
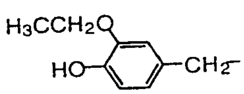
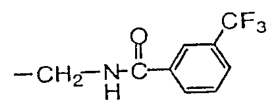
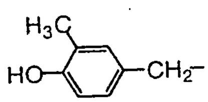
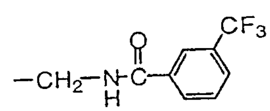
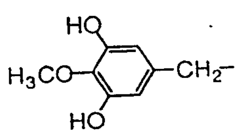
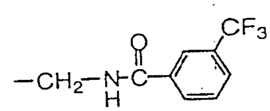
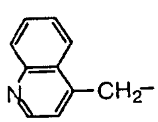
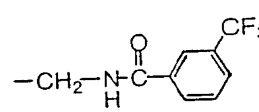
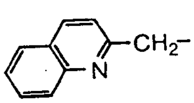
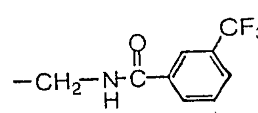
Compd. No.	$R^1R^2>$-$(CH_2)_j$-	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1706		1	2	0	R	H	
1707		1	2	0	R	H	
1708		1	2	0	R	H	
1709		1	2	0	R	H	
1710		1	2	0	R	H	
1711		1	2	0	R	H	
1712		1	2	0	R	H	
1713		1	2	0	R	H	
1714		1	2	0	R	H	
1715		1	2	0	R	H	
1716		1	2	0	R	H	

Table 1.157

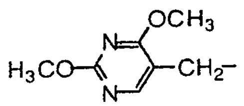
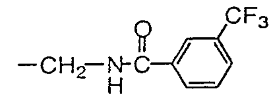
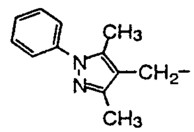
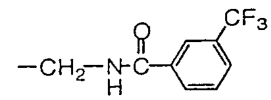
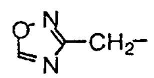
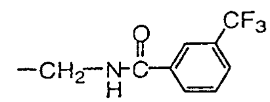
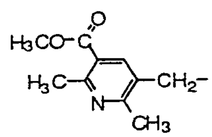
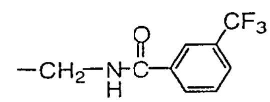
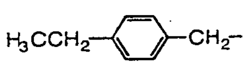
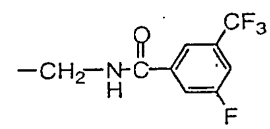
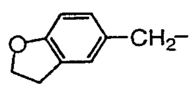
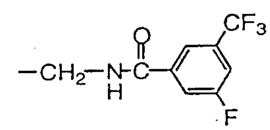
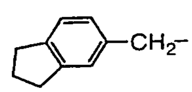
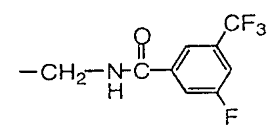
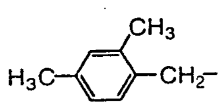
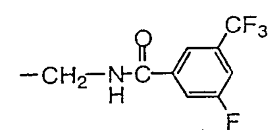
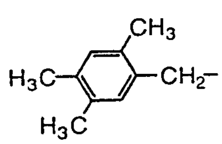
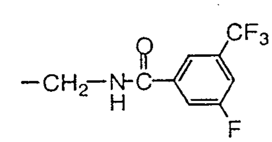
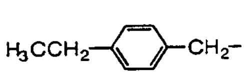
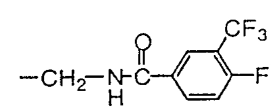
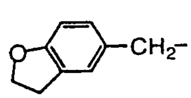
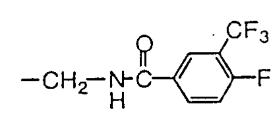
Compd. No.	$R^1R^2>$—$(CH_2)_j$—	k	m	n	chirality	R^3	—$(CH_2)_p$—$C(R^4)(R^5)$—$(CH_2)_q$—G—R^6
1717		1	2	0	R	H	
1718		1	2	0	R	H	
1719		1	2	0	R	H	
1720		1	2	0	R	H	
1721		1	2	0	R	H	
1722		1	2	0	R	H	
1723		1	2	0	R	H	
1724		1	2	0	R	H	
1725		1	2	0	R	H	
1726		1	2	0	R	H	
1727		1	2	0	R	H	

Table 1.158

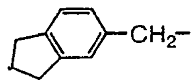
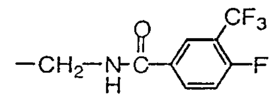
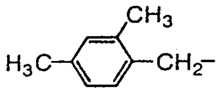
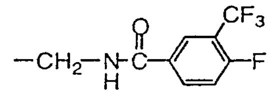
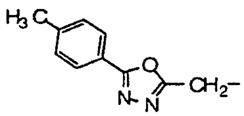
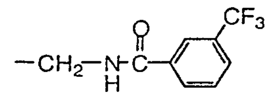
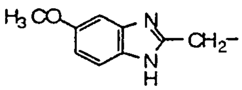
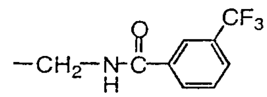
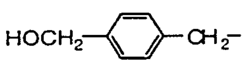
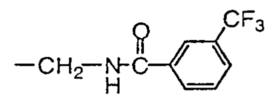
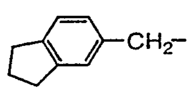
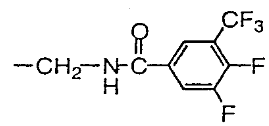
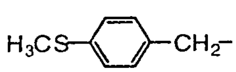
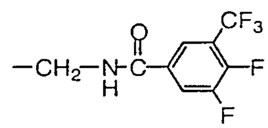
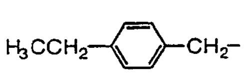
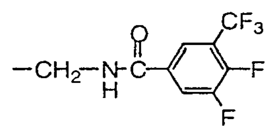
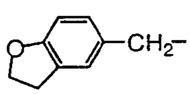
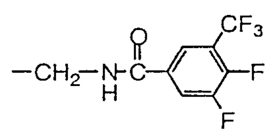
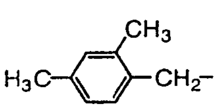
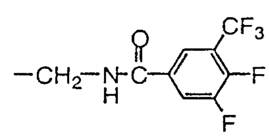
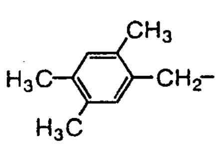
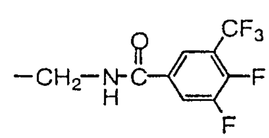
Compd. No.	R^1R^2>$-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1728		1	2	0	R	H	
1729		1	2	0	R	H	
1730		1	2	0	R	H	
1731		1	2	0	R	H	
1732		1	2	0	R	H	
1733		1	2	0	R	H	
1734		1	2	0	R	H	
1735		1	2	0	R	H	
1736		1	2	0	R	H	
1737		1	2	0	R	H	
1738		1	2	0	R	H	

Table 1.159

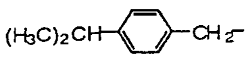
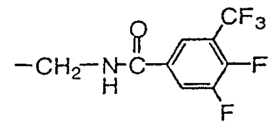
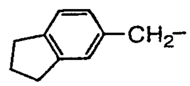
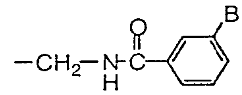
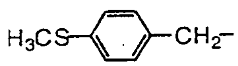
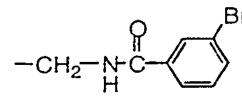
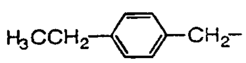
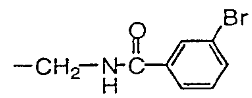
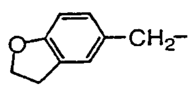
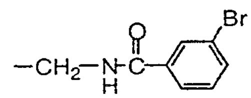
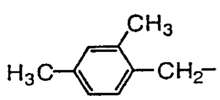
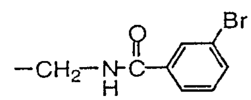
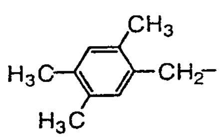
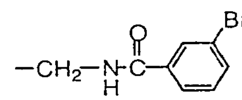
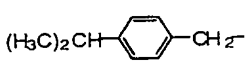
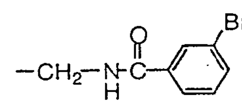
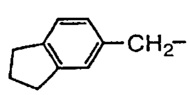
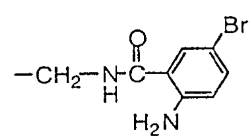
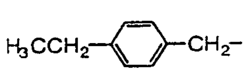
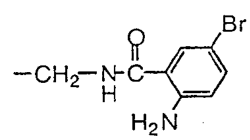
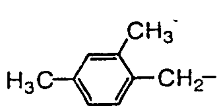
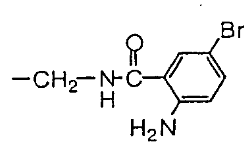
Compd. No.	R^1R^2>-$(CH_2)_j$–	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1739		1	2	0	R	H	
1740		1	2	0	R	H	
1741		1	2	0	R	H	
1742		1	2	0	R	H	
1743		1	2	0	R	H	
1744		1	2	0	R	H	
1745		1	2	0	R	H	
1746		1	2	0	R	H	
1747		1	2	0	R	H	
1748		1	2	0	R	H	
1749		1	2	0	R	H	

Table 1.160

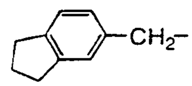
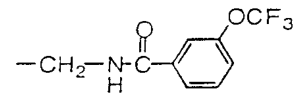
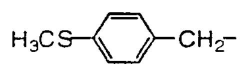
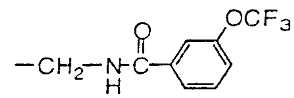
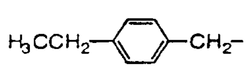
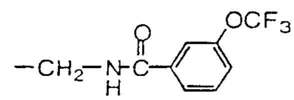
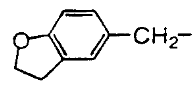
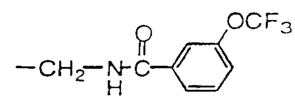
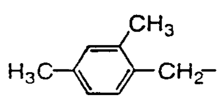
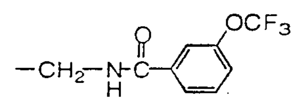
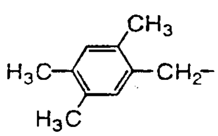
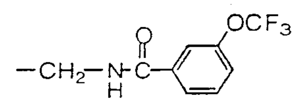
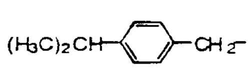
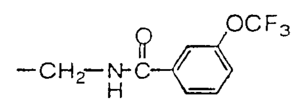
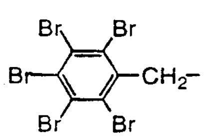
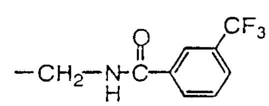
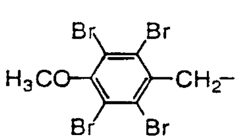
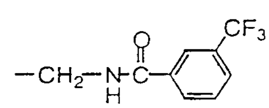
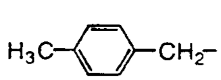
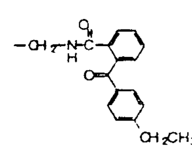
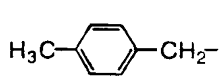
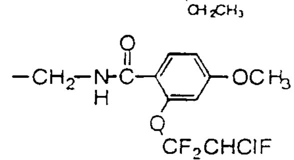
Compd. No.	$R^1R^2>(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1750		1	2	0	R	H	
1751		1	2	0	R	H	
1752		1	2	0	R	H	
1753		1	2	0	R	H	
1754		1	2	0	R	H	
1755		1	2	0	R	H	
1756		1	2	0	R	H	
1757		1	2	0	R	H	
1758		1	2	0	R	H	
1759		1	2	0	R	H	
1760		1	2	0	R	H	

Table 1.161

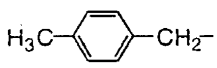
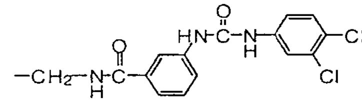
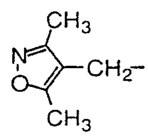
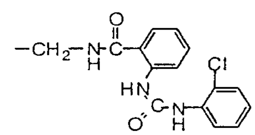
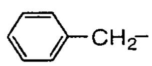
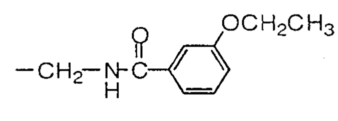
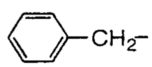
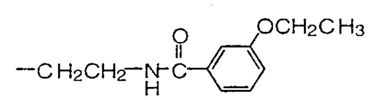
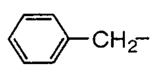
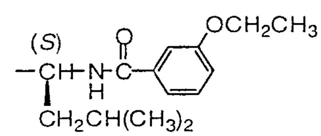
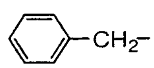
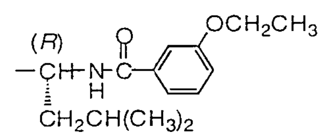
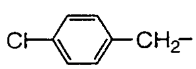
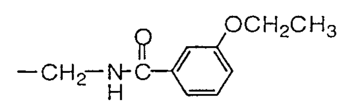
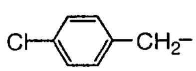
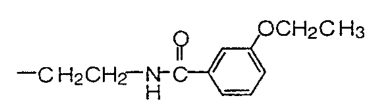
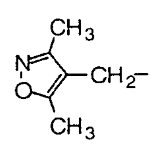
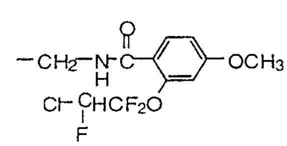
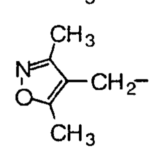
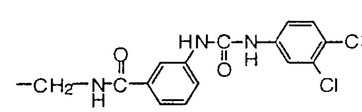
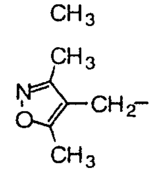
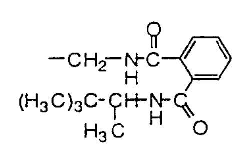
Compd. No.	$R^1R^2>$-$(CH_2)_j$-	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1761		1	2	0	R	H	
1762		1	2	0	R	H	
1763		2	2	0	-	H	
1764		2	2	0	-	H	
1765		2	2	0	-	H	
1766		2	2	0	-	H	
1767		1	3	1	-	H	
1768		1	3	1	-	H	
1769		1	2	0	R	H	
1770		1	2	0	R	H	
1771		1	2	0	R	H	

Table 1.162

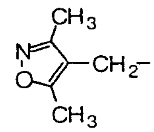
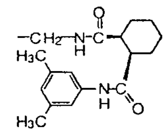
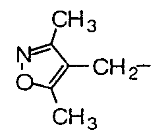
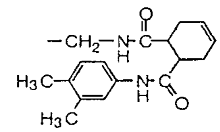
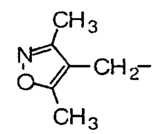
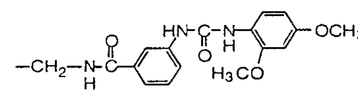
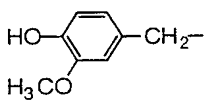
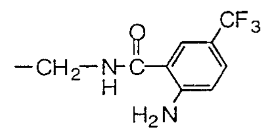
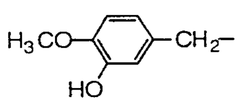
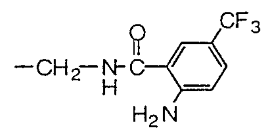
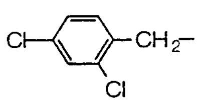
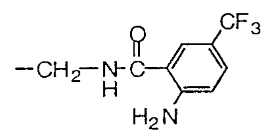
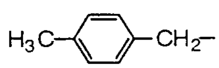
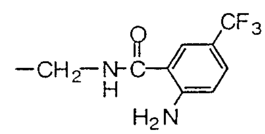
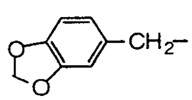
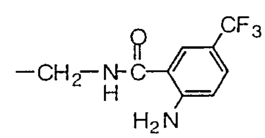
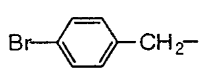
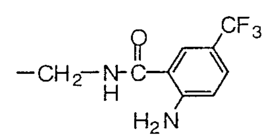
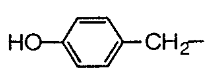
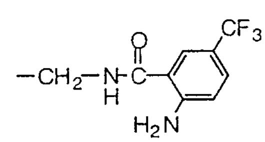
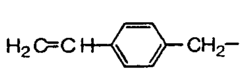
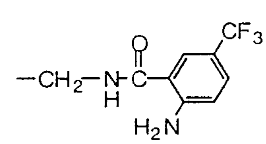
Compd. No.	$R^1R^2CH-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1772		1	2	0	R	H	
1773		1	2	0	R	H	
1774		1	2	0	R	H	
1775		1	2	0	R	H	
1776		1	2	0	R	H	
1777		2	2	1	-	H	
1778		2	2	1	-	H	
1779		2	2	1	-	H	
1780		2	2	1	-	H	
1781		2	2	1	-	H	
1782		2	2	1	-	H	

Table 1.163

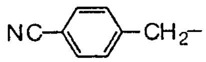
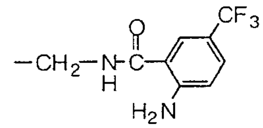
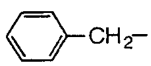
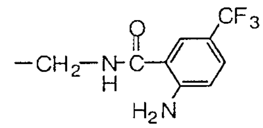
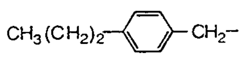
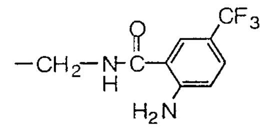
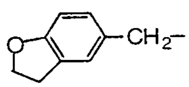
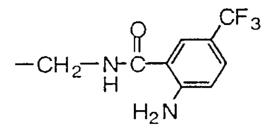
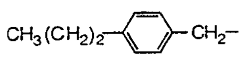
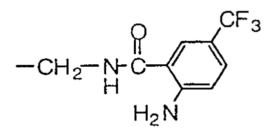
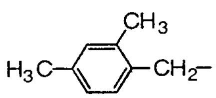
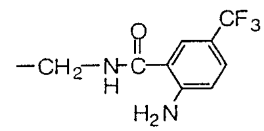
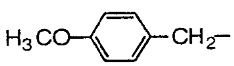
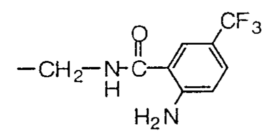
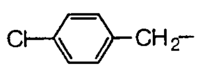
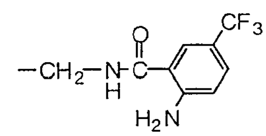
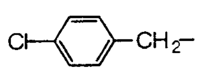
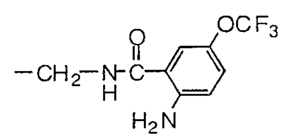
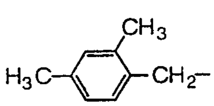
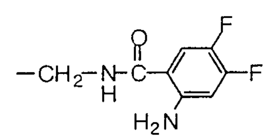
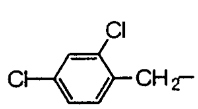
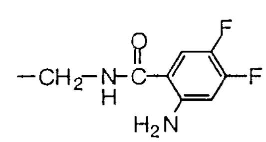
Compd. No.	$R^1R^2>-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1783		2	2	1	-	H	
1784		2	2	1	-	H	
1785		2	2	1	-	H	
1786		2	2	1	-	H	
1787		1	2	0	R	H	
1788		2	2	1	-	H	
1789		2	2	1	-	H	
1790		1	2	0	S	H	
1791		1	2	0	S	H	
1792		2	2	1	-	H	
1793		2	2	1	-	H	

Table 1.164

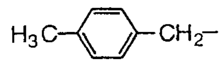
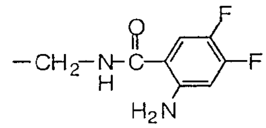
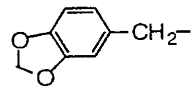
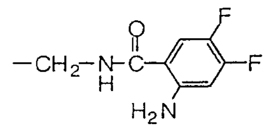
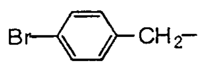
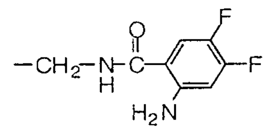
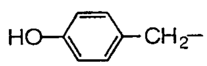
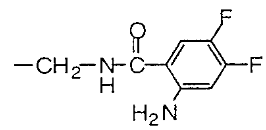
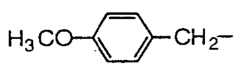
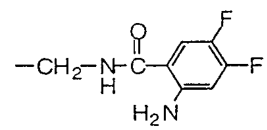
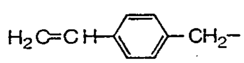
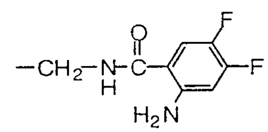
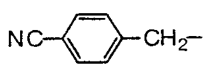
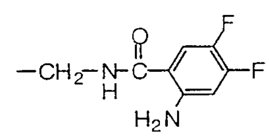
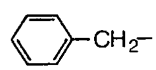
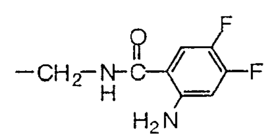
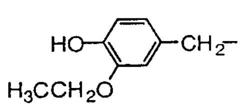
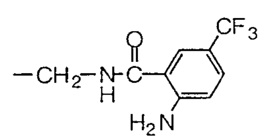
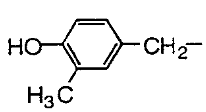
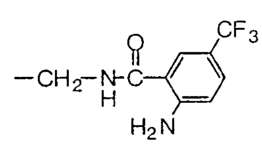
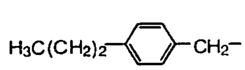
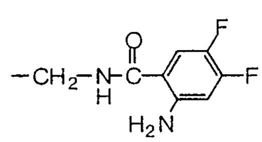
Compd. No.	$R^1R^2{>}(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1794		2	2	1	-	H	
1795		2	2	1	-	H	
1796		2	2	1	-	H	
1797		2	2	1	-	H	
1798		2	2	1	-	H	
1799		2	2	1	-	H	
1800		2	2	1	-	H	
1801		2	2	1	-	H	
1802		1	2	0	R	H	
1803		1	2	0	R	H	
1804		2	2	1	-	H	

Table 1.165

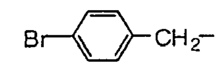
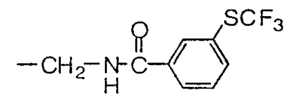
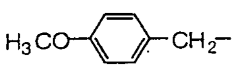
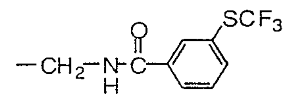
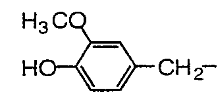
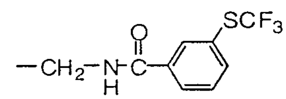
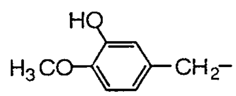
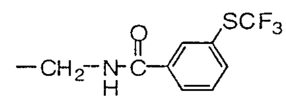
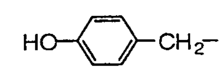
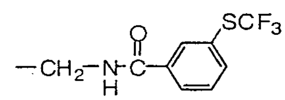
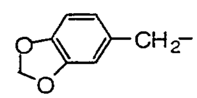
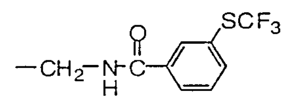
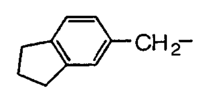
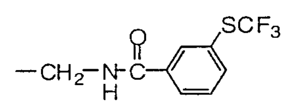
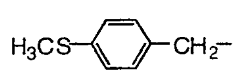
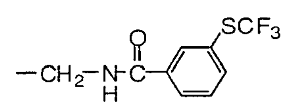
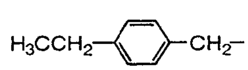
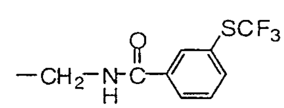
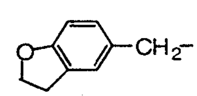
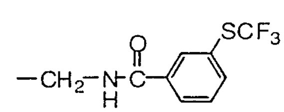
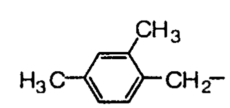
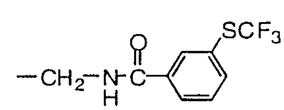
Compd. No.	$R^1R^2>$-$(CH_2)_j$-	k	m	n	chirality	R^3	-$(CH_2)_p$-$C(R^4)(R^5)$-$(CH_2)_q$-G-R^6
1805		1	2	0	R	H	
1806		1	2	0	R	H	
1807		1	2	0	R	H	
1808		1	2	0	R	H	
1809		1	2	0	R	H	
1810		1	2	0	R	H	
1811		1	2	0	R	H	
1812		1	2	0	R	H	
1813		1	2	0	R	H	
1814		1	2	0	R	H	
1815		1	2	0	R	H	

Table 1.166

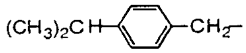
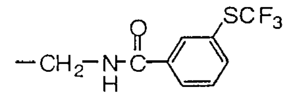
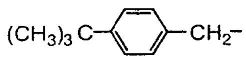
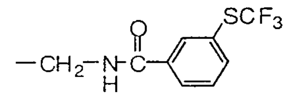
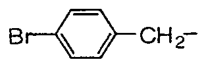
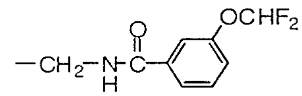
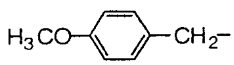
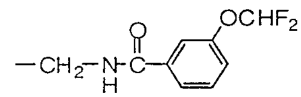
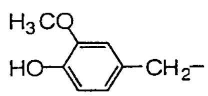
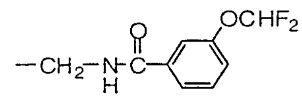
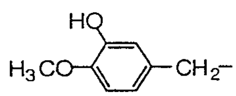
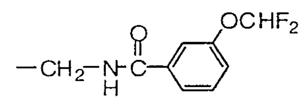
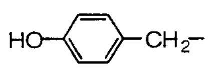
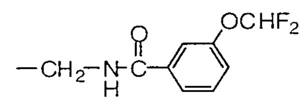
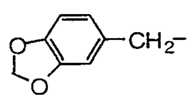
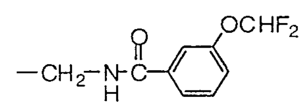
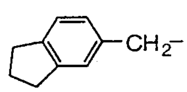
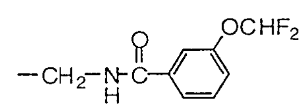
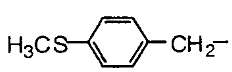
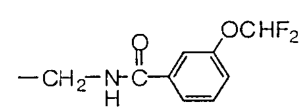
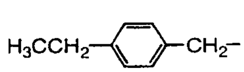
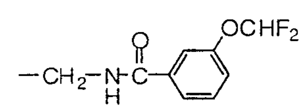
Compd. No.	$R^1R^2>$—$(CH_2)_j$—	k	m	n	chirality	R^3	—$(CH_2)_p$—$C(R^4)(R^5)$—$(CH_2)_q$—G—R^6
1816		1	2	0	R	H	
1817		1	2	0	R	H	
1818		1	2	0	R	H	
1819		1	2	0	R	H	
1820		1	2	0	R	H	
1821		1	2	0	R	H	
1822		1	2	0	R	H	
1823		1	2	0	R	H	
1824		1	2	0	R	H	
1825		1	2	0	R	H	
1826		1	2	0	R	H	

Table 1.167

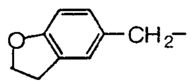
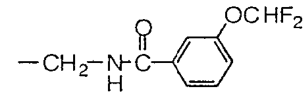
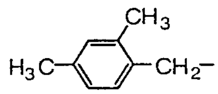
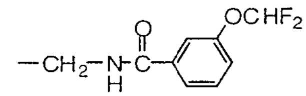
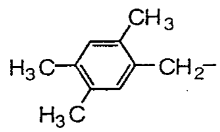
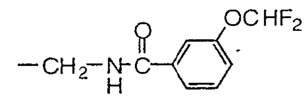
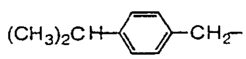
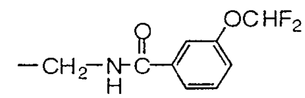
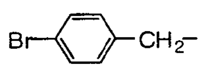
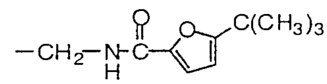
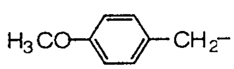
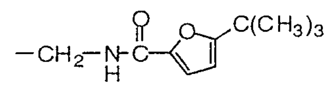
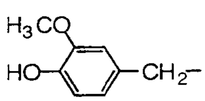
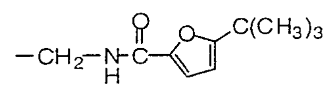
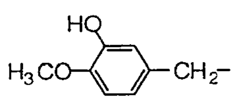
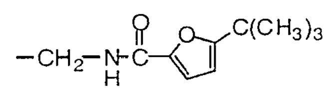
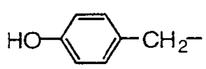
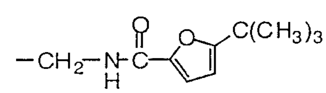
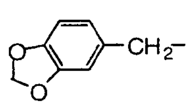
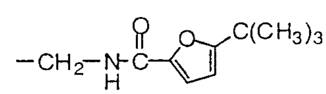
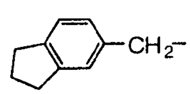
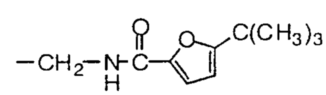
Compd. No.	$R^1R^2{>}(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1827		1	2	0	R	H	
1828		1	2	0	R	H	
1829		1	2	0	R	H	
1830		1	2	0	R	H	
1831		1	2	0	R	H	
1832		1	2	0	R	H	
1833		1	2	0	R	H	
1834		1	2	0	R	H	
1835		1	2	0	R	H	
1836		1	2	0	R	H	
1837		1	2	0	R	H	

Table 1.168

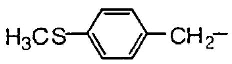
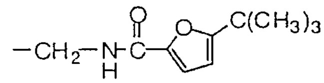
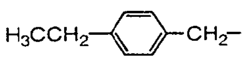
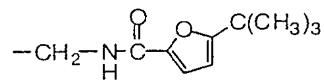
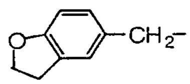
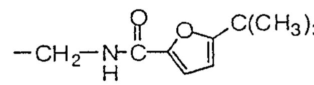
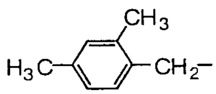
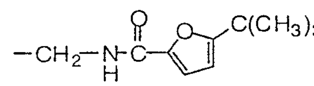
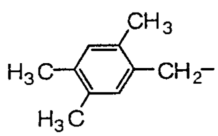
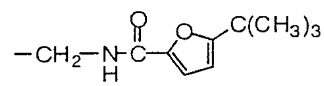
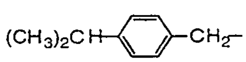
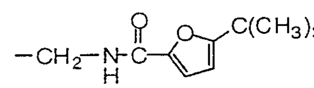
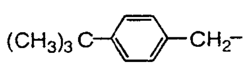
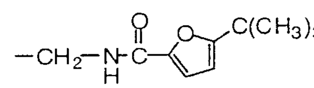
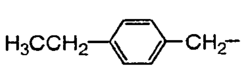
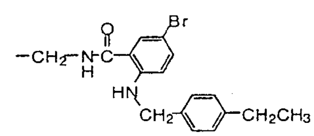
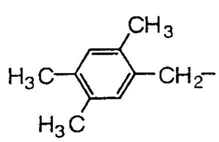
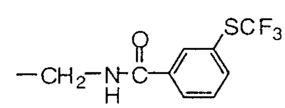
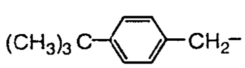
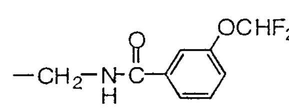
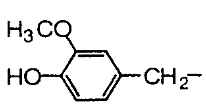
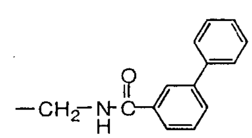
Compd. No.	$R^1R^2>(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1838		1	2	0	R	H	
1839		1	2	0	R	H	
1840		1	2	0	R	H	
1841		1	2	0	R	H	
1842		1	2	0	R	H	
1843		1	2	0	R	H	
1844		1	2	0	R	H	
1845		1	2	0	R	H	
1846		1	2	0	R	H	
1847		1	2	0	R	H	
1848		1	2	0	R	H	

Table 1.169

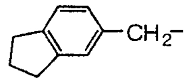
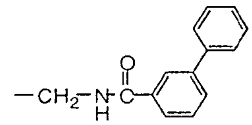
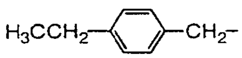
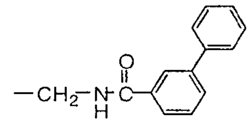
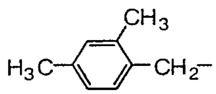
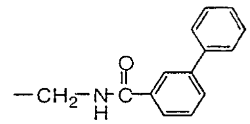
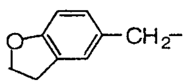
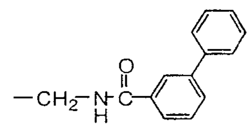
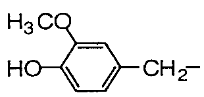
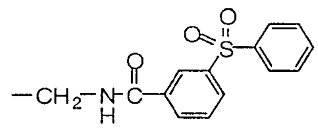
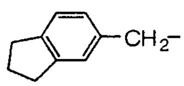
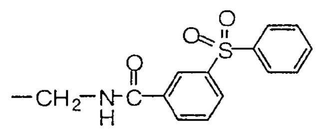
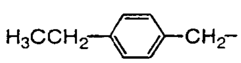
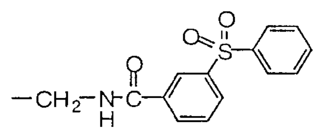
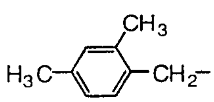
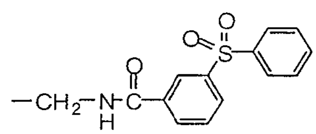
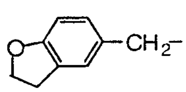
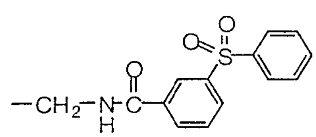
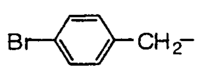
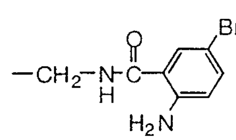
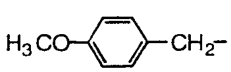
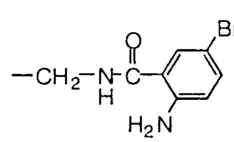
Compd. No.	$R^1R^2{>}$$-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1849		1	2	0	R	H	
1850		1	2	0	R	H	
1851		1	2	0	R	H	
1852		1	2	0	R	H	
1853		1	2	0	R	H	
1854		1	2	0	R	H	
1855		1	2	0	R	H	
1856		1	2	0	R	H	
1857		1	2	0	R	H	
1858		1	2	0	R	H	
1859		1	2	0	R	H	

Table 1.170

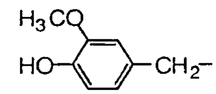
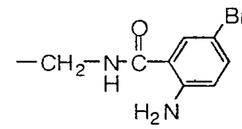
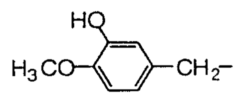
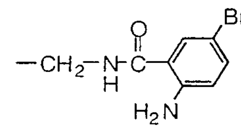
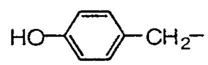
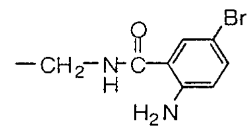
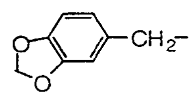
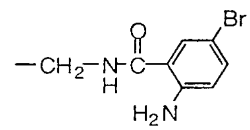
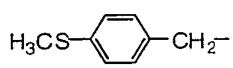
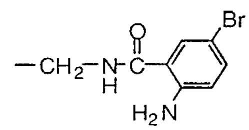
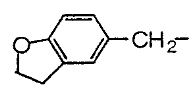
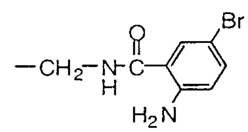
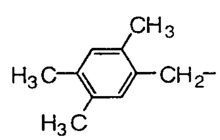
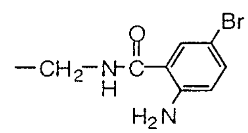
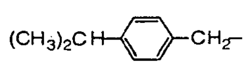
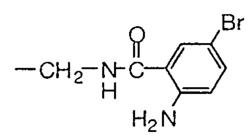
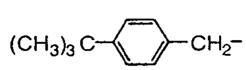
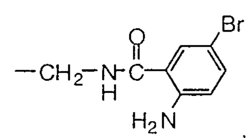
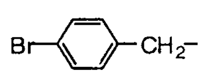
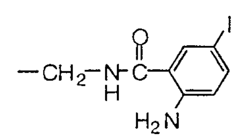
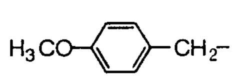
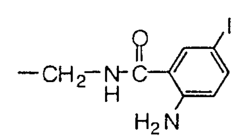
Compd. No.	$R^1R^2>$-$(CH_2)_j$–	k	m	n	chirality	R^3	–$(CH_2)_p$–$C(R^4)(R^5)$–$(CH_2)_q$–G–R^6
1860		1	2	0	R	H	
1861		1	2	0	R	H	
1862		1	2	0	R	H	
1863		1	2	0	R	H	
1864		1	2	0	R	H	
1865		1	2	0	R	H	
1866		1	2	0	R	H	
1867		1	2	0	R	H	
1868		1	2	0	R	H	
1869		1	2	0	R	H	
1870		1	2	0	R	H	

Table 1.171

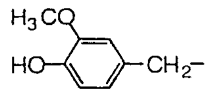
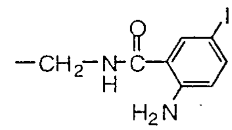
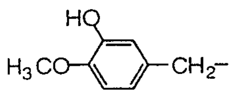
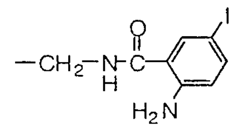
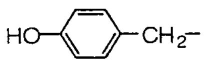
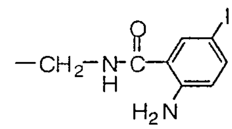
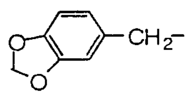
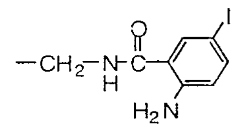
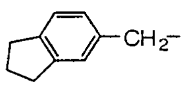
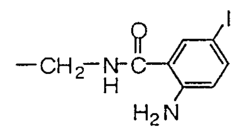
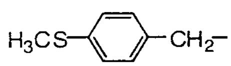
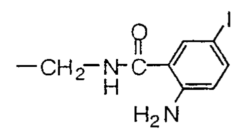
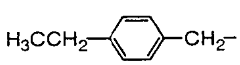
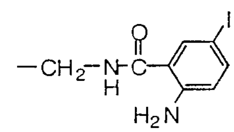
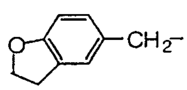
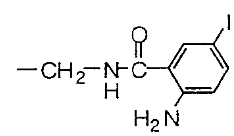
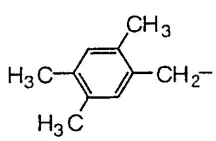
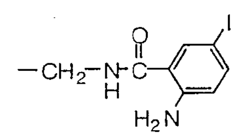
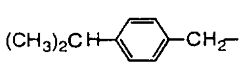
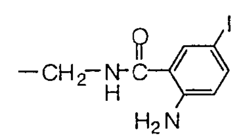
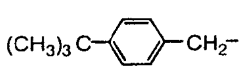
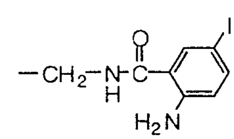
Compd. No.	R^1R^2>-$(CH_2)_j$–	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1871		1	2	0	R	H	
1872		1	2	0	R	H	
1873		1	2	0	R	H	
1874		1	2	0	R	H	
1875		1	2	0	R	H	
1876		1	2	0	R	H	
1877		1	2	0	R	H	
1878		1	2	0	R	H	
1879		1	2	0	R	H	
1880		1	2	0	R	H	
1881		1	2	0	R	H	

Table 1.172

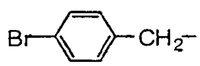
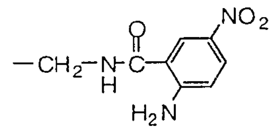
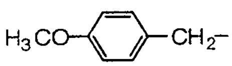
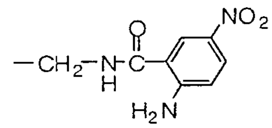
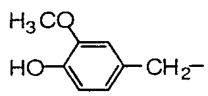
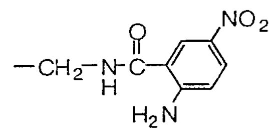
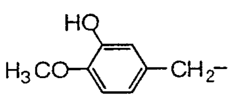
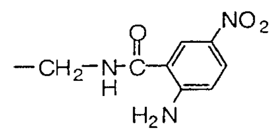
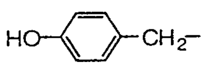
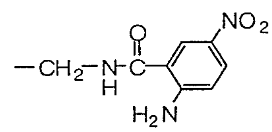
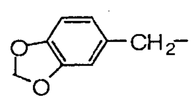
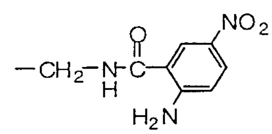
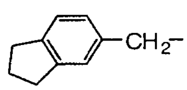
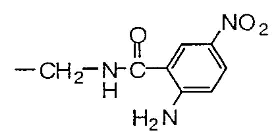
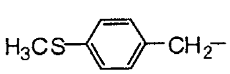
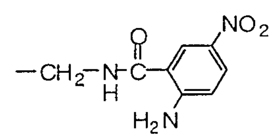
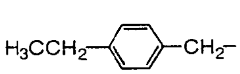
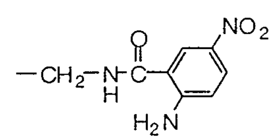
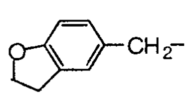
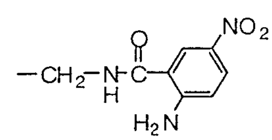
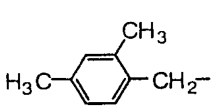
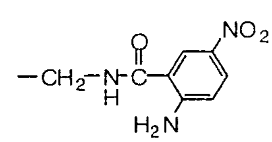
Compd. No.	R^1R^2>-$(CH_2)_j$-	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1882		1	2	0	R	H	
1883		1	2	0	R	H	
1884		1	2	0	R	H	
1885		1	2	0	R	H	
1886		1	2	0	R	H	
1887		1	2	0	R	H	
1888		1	2	0	R	H	
1889		1	2	0	R	H	
1890		1	2	0	R	H	
1891		1	2	0	R	H	
1892		1	2	0	R	H	

Table 1.173

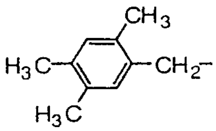
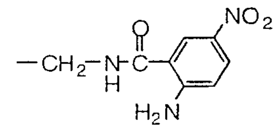
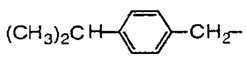
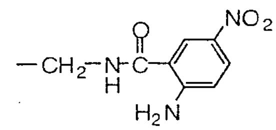
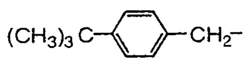
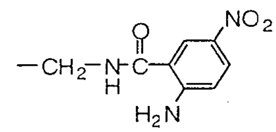
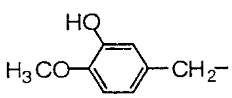
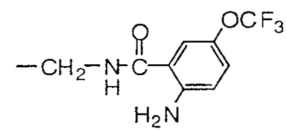
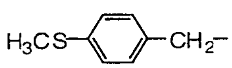
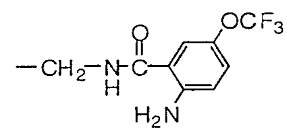
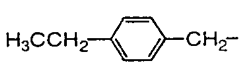
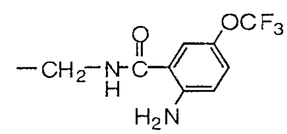
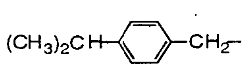
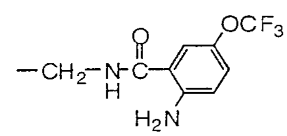
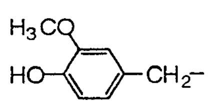
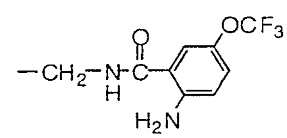
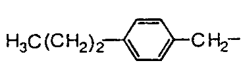
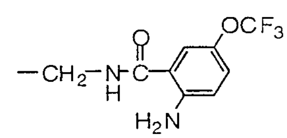
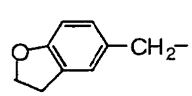
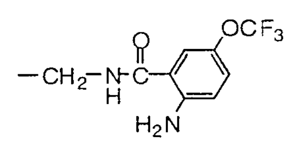
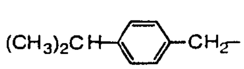
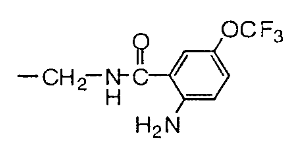
Compd. No.	$R^1R^2>(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1893		1	2	0	R	H	
1894		1	2	0	R	H	
1895		1	2	0	R	H	
1896		1	2	0	R	H	
1897		1	2	0	R	H	
1898		1	2	0	R	H	
1899		1	2	0	R	H	
1900		1	2	0	R	H	
1901		1	2	0	R	H	
1902		1	2	0	R	H	
1903		2	2	1	-	H	

Table 1.174

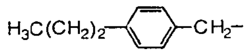
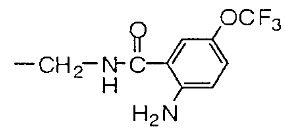
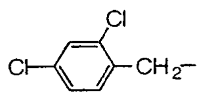
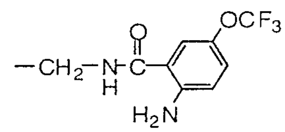
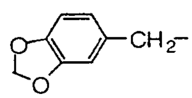
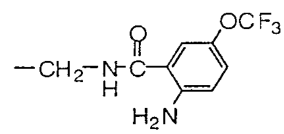
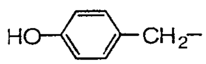
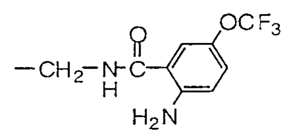
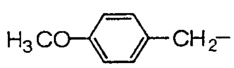
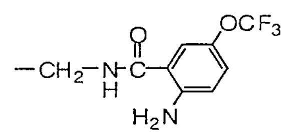
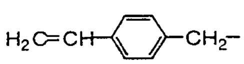
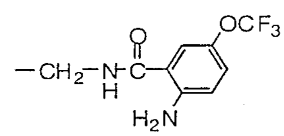
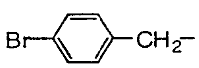
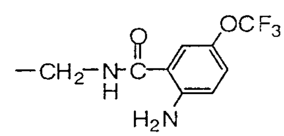
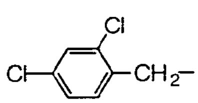
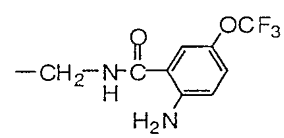
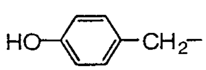
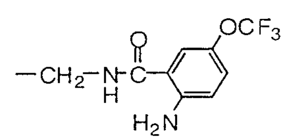
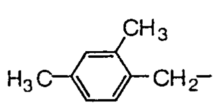
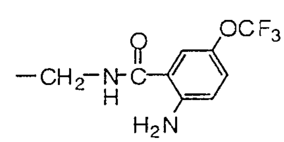
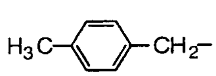
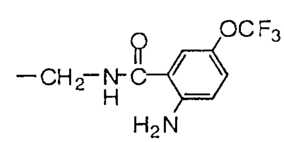
Compd. No.	$R^1R^2{>}(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1904		2	2	1	-	H	
1905		1	2	0	R	H	
1906		1	2	0	R	H	
1907		1	2	0	R	H	
1908		1	2	0	R	H	
1909		1	2	0	R	H	
1910		2	2	1	-	H	
1911		2	2	1	-	H	
1912		2	2	1	-	H	
1913		2	2	1	-	H	
1914		2	2	1	-	H	

Table 1.175

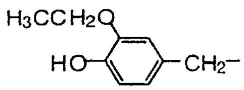
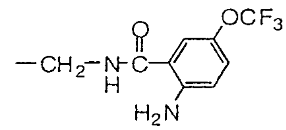
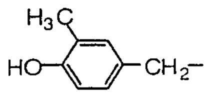
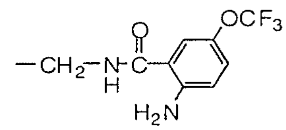
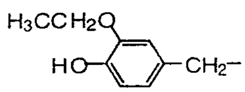
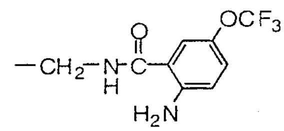
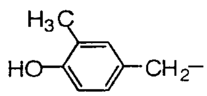
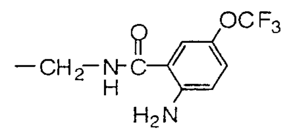
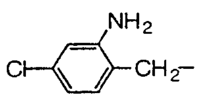
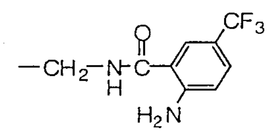
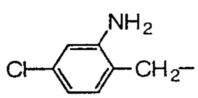
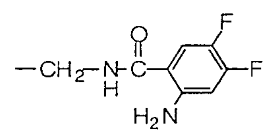
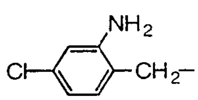
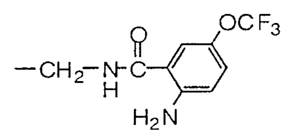
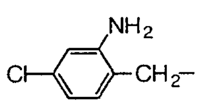
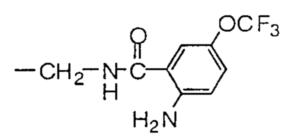
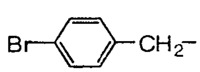
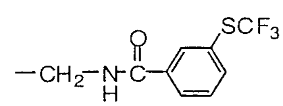
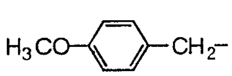
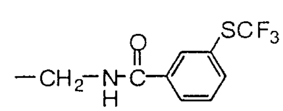
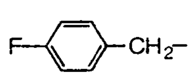
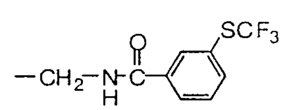
Compd. No.	R^1R^2>-$(CH_2)_j$-	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1915		1	2	0	R	H	
1916		1	2	0	R	H	
1917		2	2	1	-	H	
1918		2	2	1	-	H	
1919		2	2	1	-	H	
1920		2	2	1	-	H	
1921		1	2	0	R	H	
1922		2	2	1	-	H	
1923		2	2	1	-	H	
1924		2	2	1	-	H	
1925		2	2	1	-	H	

Table 1.176

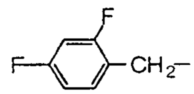
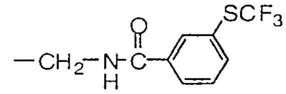
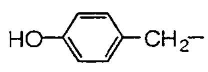
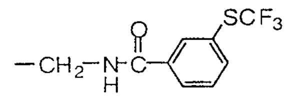
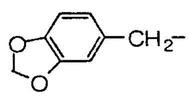
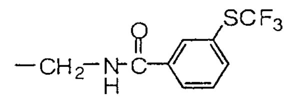
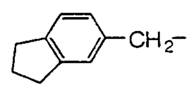
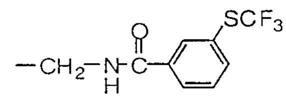
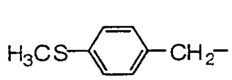
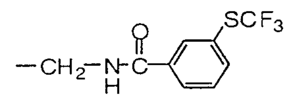
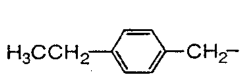
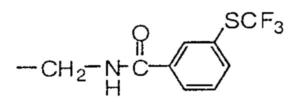
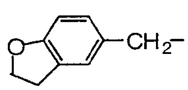
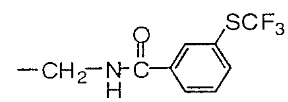
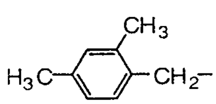
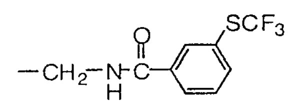
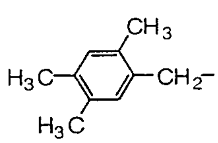
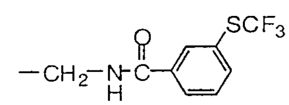
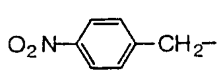
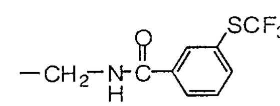
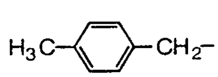
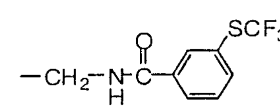
Compd. No.	$R^1R^2{>}\text{-}(CH_2)_j\text{-}$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1926		2	2	1	-	H	
1927		2	2	1	-	H	
1928		2	2	1	-	H	
1929		2	2	1	-	H	
1930		2	2	1	-	H	
1931		2	2	1	-	H	
1932		2	2	1	-	H	
1933		2	2	1	-	H	
1934		2	2	1	-	H	
1935		2	2	1	-	H	
1936		2	2	1	-	H	

Table 1.177

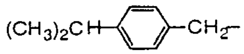
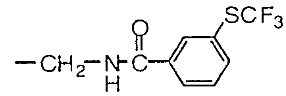
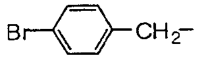
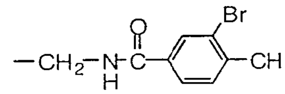
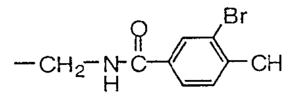
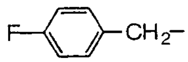
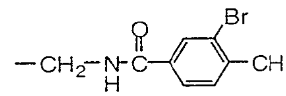
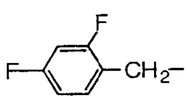
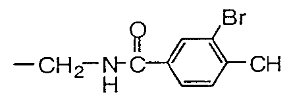
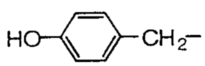
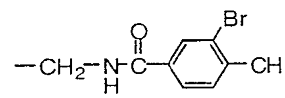
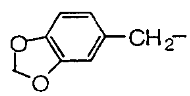
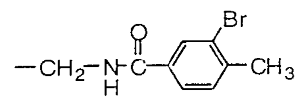
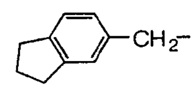
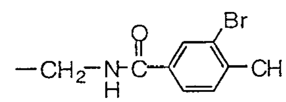
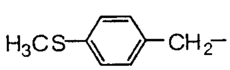
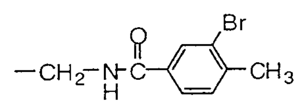
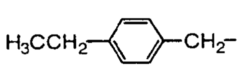
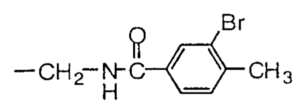
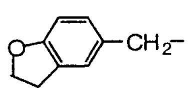
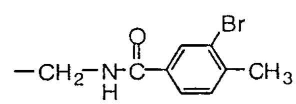
Compd. No.	$R^1R^2>$–$(CH_2)_j$–	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1937		2	2	1	-	H	
1938		2	2	1	-	H	
1939		2	2	1	-	H	
1940		2	2	1	-	H	
1941		2	2	1	-	H	
1942		2	2	1	-	H	
1943		2	2	1	-	H	
1944		2	2	1	-	H	
1945		2	2	1	-	H	
1946		2	2	1	-	H	
1947		2	2	1	-	H	

Table 1.178

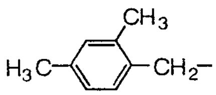
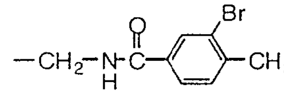
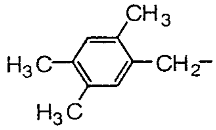
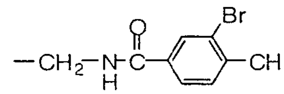
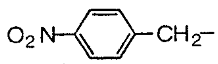
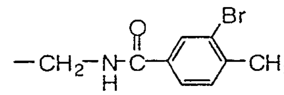
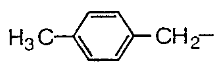
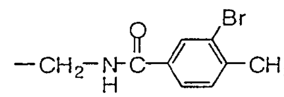
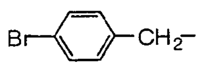
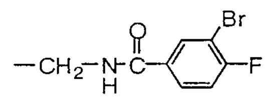
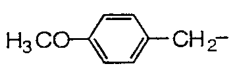
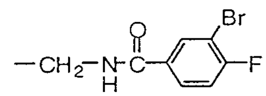
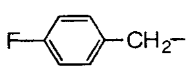
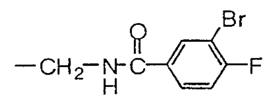
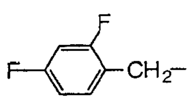
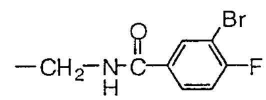
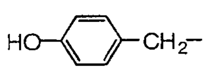
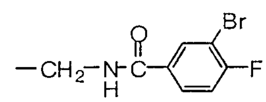
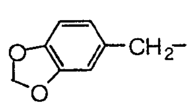
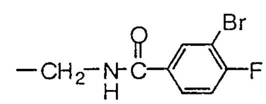
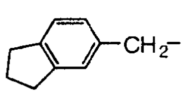
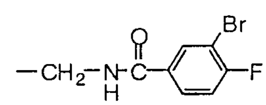
Compd. No.	R^1, R^2 $>(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1948		2	2	1	-	H	
1949		2	2	1	-	H	
1950		2	2	1	-	H	
1951		2	2	1	-	H	
1952		2	2	1	-	H	
1953		2	2	1	-	H	
1954		2	2	1	-	H	
1955		2	2	1	-	H	
1956		2	2	1	-	H	
1957		2	2	1	-	H	
1958		2	2	1	-	H	

Table 1.179

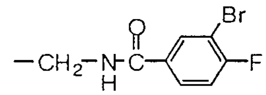
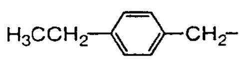
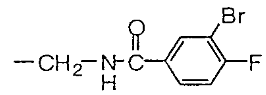
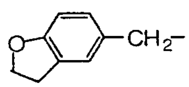
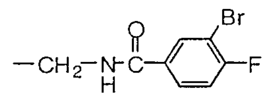
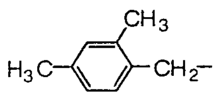
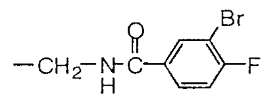
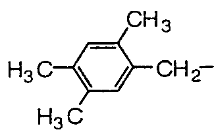
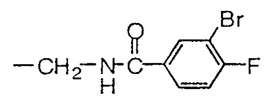
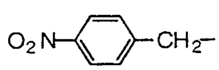
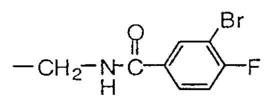
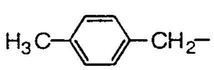
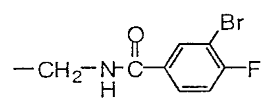
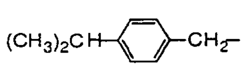
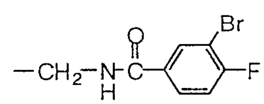
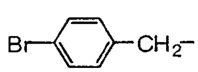
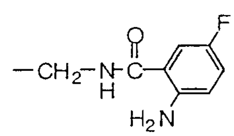
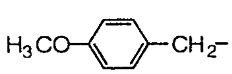
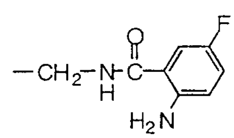
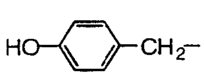
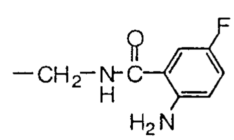
Compd. No.	$R^1R^2>-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-\overset{R^4}{\underset{R^5}{\vert}}-(CH_2)_q-G-R^6$
1959		2	2	1	-	H	
1960		2	2	1	-	H	
1961		2	2	1	-	H	
1962		2	2	1	-	H	
1963		2	2	1	-	H	
1964		2	2	1	-	H	
1965		2	2	1	-	H	
1966		2	2	1	-	H	
1967		2	2	1	-	H	
1968		2	2	1	-	H	
1969		2	2	1	-	H	

Table 1.180

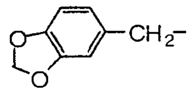
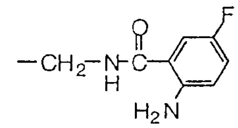
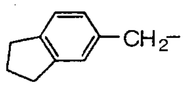
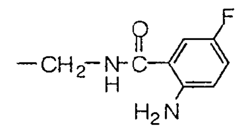
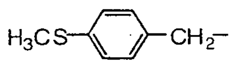
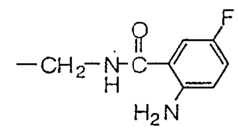
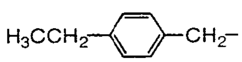
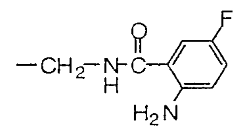
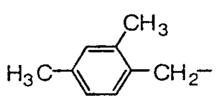
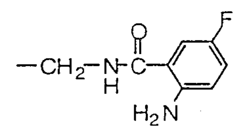
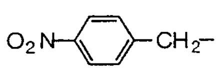
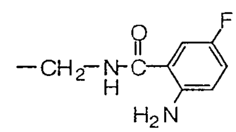
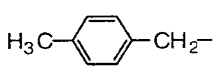
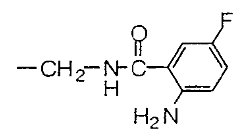
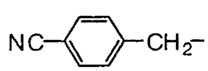
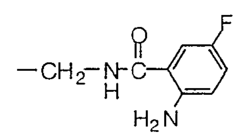
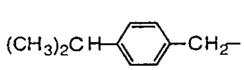
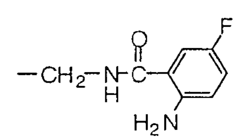
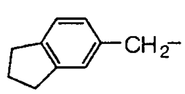
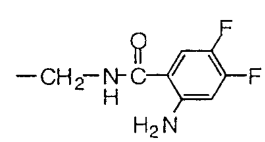
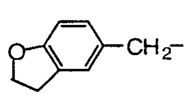
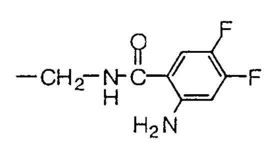
Compd. No.	$R^1R^2>-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1970		2	2	1	-	H	
1971		2	2	1	-	H	
1972		2	2	1	-	H	
1973		2	2	1	-	H	
1974		2	2	1	-	H	
1975		2	2	1	-	H	
1976		2	2	1	-	H	
1977		2	2	1	-	H	
1978		2	2	1	-	H	
1979		2	2	1	-	H	
1980		2	2	1	-	H	

Table 1.181

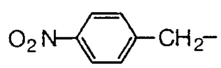
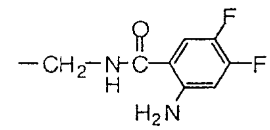
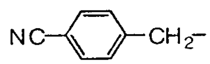
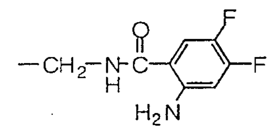
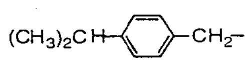
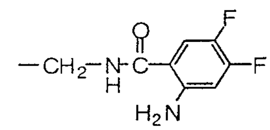
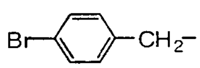
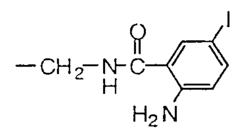
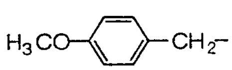
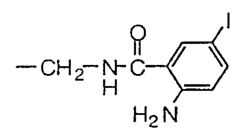
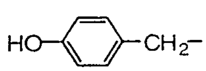
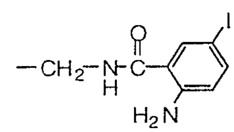
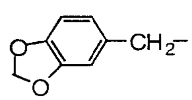
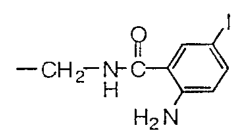
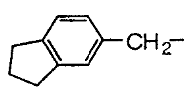
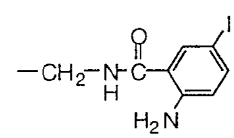
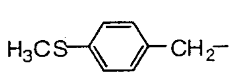
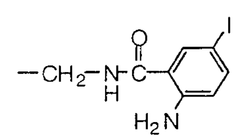
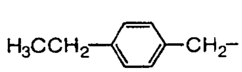
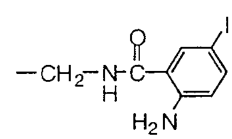
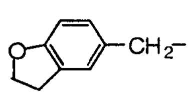
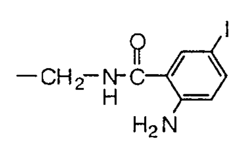
Compd. No.	$R^1R^2>$-$(CH_2)_j$-	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1981		2	2	1	-	H	
1982		2	2	1	-	H	
1983		2	2	1	-	H	
1984		2	2	1	-	H	
1985		2	2	1	-	H	
1986		2	2	1	-	H	
1987		2	2	1	-	H	
1988		2	2	1	-	H	
1989		2	2	1	-	H	
1990		2	2	1	-	H	
1991		2	2	1	-	H	

Table 1.182

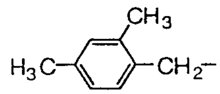
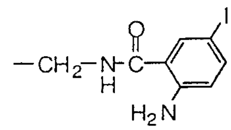
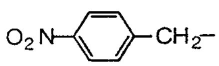
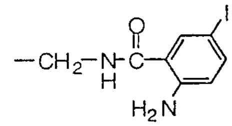
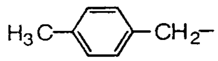
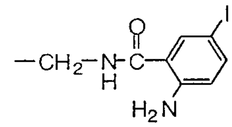
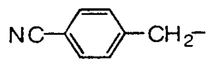
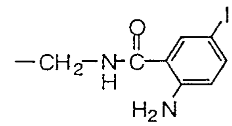
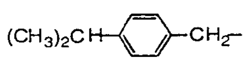
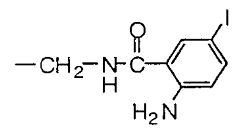
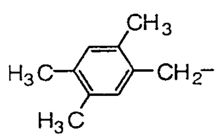
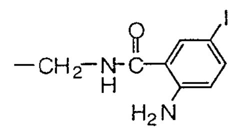
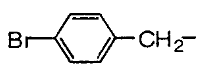
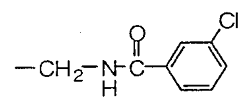
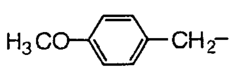
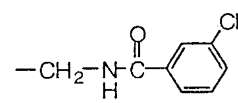
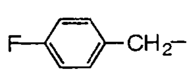
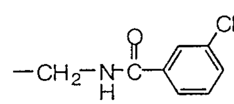
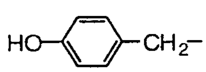
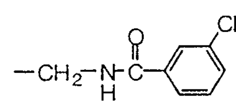
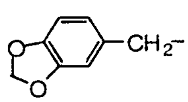
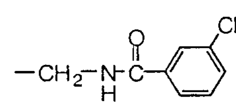
Compd. No.	$R^1R^2>(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1992		2	2	1	-	H	
1993		2	2	1	-	H	
1994		2	2	1	-	H	
1995		2	2	1	-	H	
1996		2	2	1	-	H	
1997		2	2	1	-	H	
1998		2	2	1	-	H	
1999		2	2	1	-	H	
2000		2	2	1	-	H	
2001		2	2	1	-	H	
2002		2	2	1	-	H	

Table 1.183

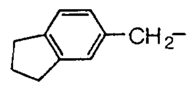
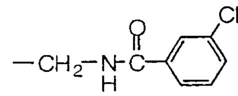
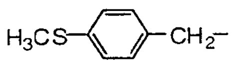
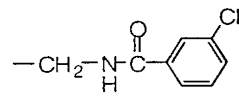
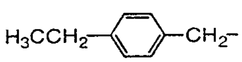
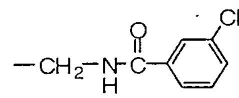
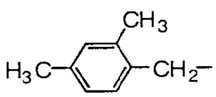
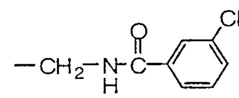
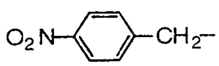
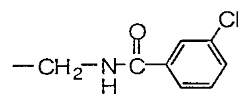
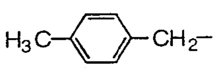
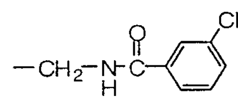
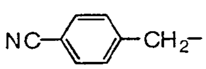
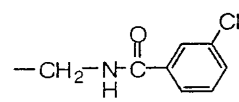
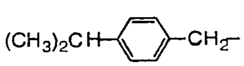
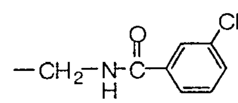
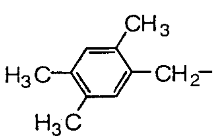
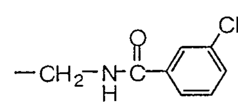
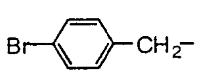
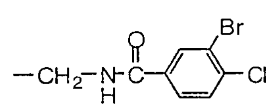
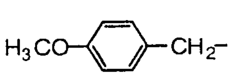
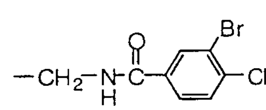
Compd. No.	$R^1R^2{>}\text{-}(CH_2)_j\text{-}$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
2003		2	2	1	-	H	
2004		2	2	1	-	H	
2005		2	2	1	-	H	
2006		2	2	1	-	H	
2007		2	2	1	-	H	
2008		2	2	1	-	H	
2009		2	2	1	-	H	
2010		2	2	1	-	H	
2011		2	2	1	-	H	
2012		2	2	1	-	H	
2013		2	2	1	-	H	

Table 1.184

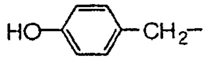
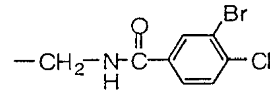
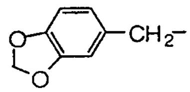
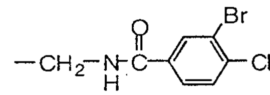
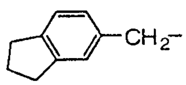
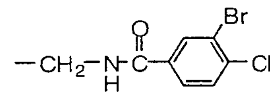
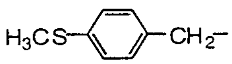
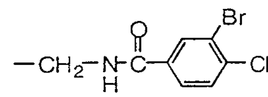
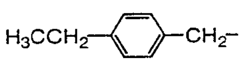
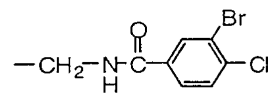
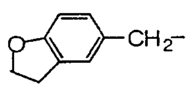
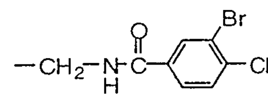
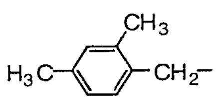
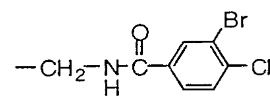
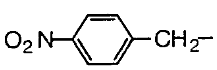
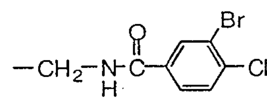
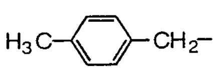
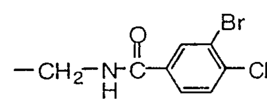
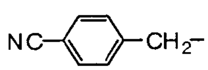
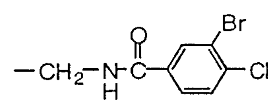
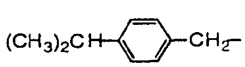
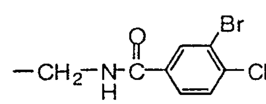
Compd. No.	$R^1R^2>-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
2014		2	2	1	-	H	
2015		2	2	1	-	H	
2016		2	2	1	-	H	
2017		2	2	1	-	H	
2018		2	2	1	-	H	
2019		2	2	1	-	H	
2020		2	2	1	-	H	
2021		2	2	1	-	H	
2022		2	2	1	-	H	
2023		2	2	1	-	H	
2024		2	2	1	-	H	

Table 1.185

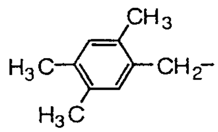
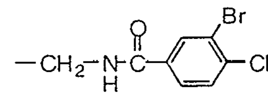
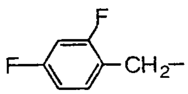
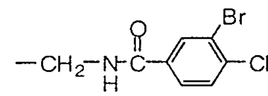
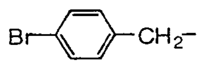
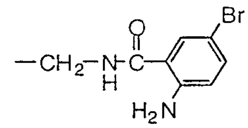
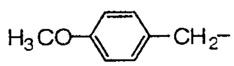
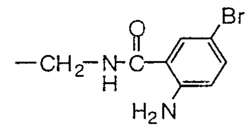
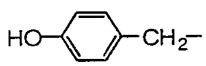
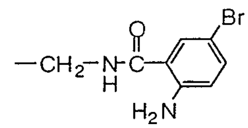
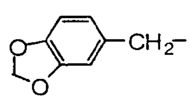
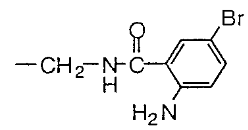
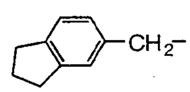
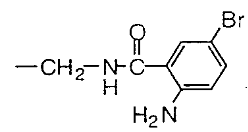
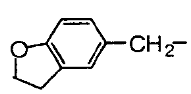
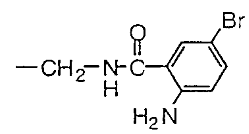
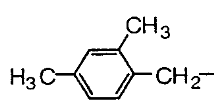
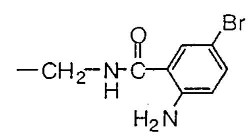
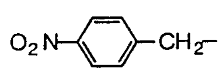
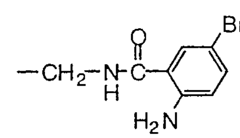
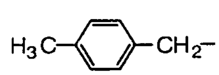
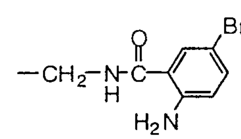
Compd. No.	$R^1R^2>-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
2025		2	2	1	-	H	
2026		2	2	1	-	H	
2027		2	2	1	-	H	
2028		2	2	1	-	H	
2029		2	2	1	-	H	
2030		2	2	1	-	H	
2031		2	2	1	-	H	
2032		2	2	1	-	H	
2033		2	2	1	-	H	
2034		2	2	1	-	H	
2035		2	2	1	-	H	

Table 1.186

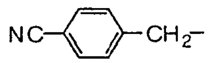
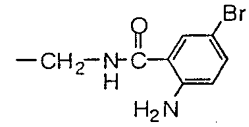
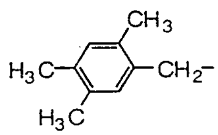
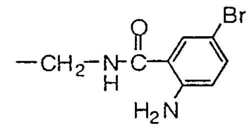
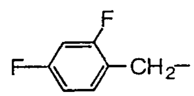
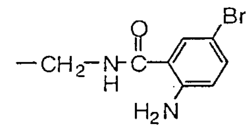
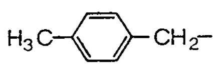
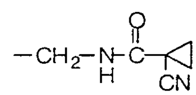
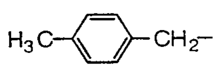
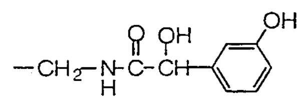
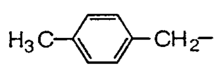
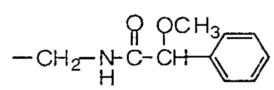
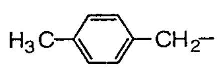
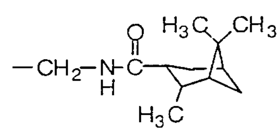
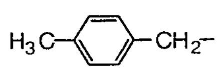
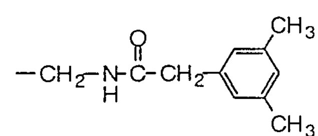
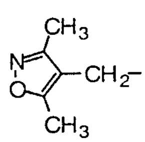
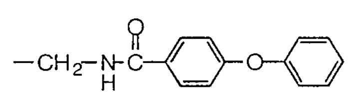
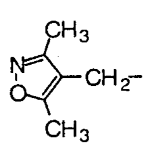
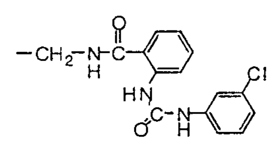
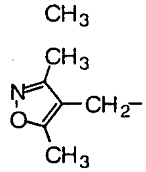
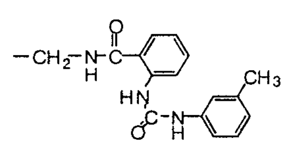
Compd. No.	$R^1R^2>$–$(CH_2)_j$–	k	m	n	chirality	R^3	–$(CH_2)_p$–$C(R^4)(R^5)$–$(CH_2)_q$–G–R^6
2036		2	2	1	-	H	
2037		2	2	1	-	H	
2038		2	2	1	-	H	
2039		2	2	1	-	H	
2040		1	2	0	R	H	
2041		1	2	0	R	H	
2042		1	2	0	R	H	
2043		1	2	0	R	H	
2044		1	2	0	R	H	
2045		1	2	0	R	H	
2046		1	2	0	R	H	

Table 1.187

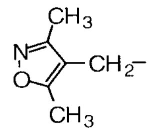
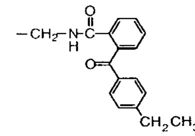
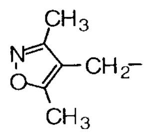
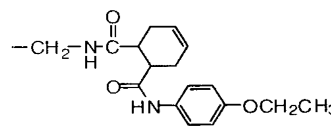
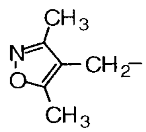
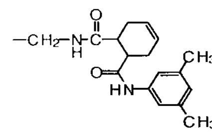
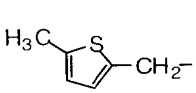
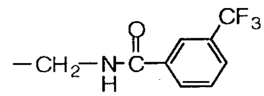
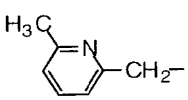
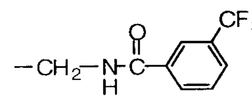
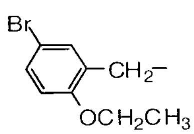
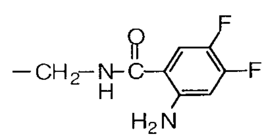
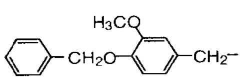
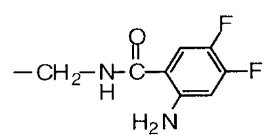
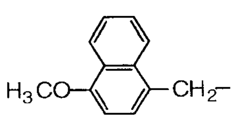
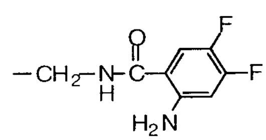
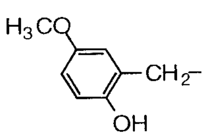
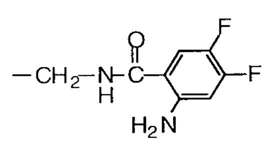
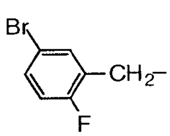
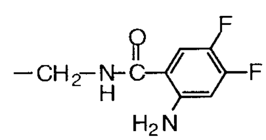
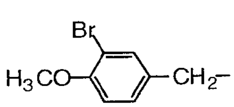
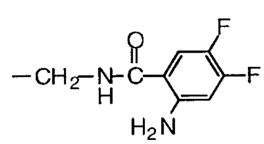
Compd. No.	R^1R^2>-$(CH_2)_j$–	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
2047		1	2	0	R	H	
2048		1	2	0	R	H	
2049		1	2	0	R	H	
2050		1	2	0	R	H	
2051		1	2	0	R	H	
2052		2	2	1	-	H	
2053		2	2	1	-	H	
2054		2	2	1	-	H	
2055		2	2	1	-	H	
2056		2	2	1	-	H	
2057		2	2	1	-	H	

Table 1.188

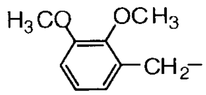
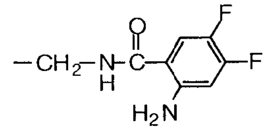
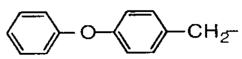
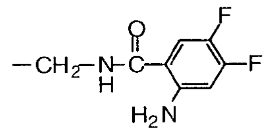
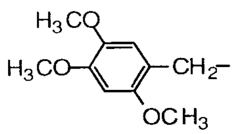
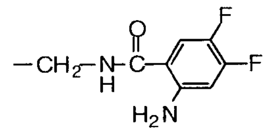
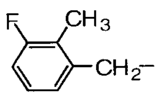
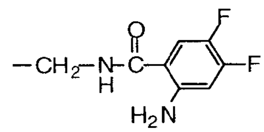
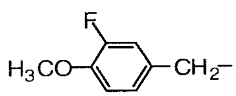
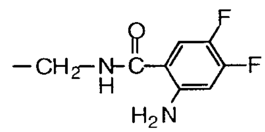
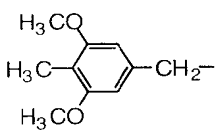
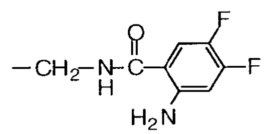
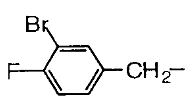
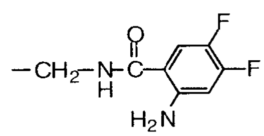
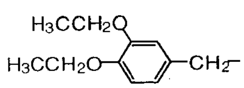
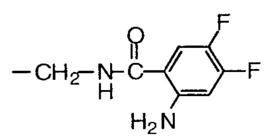
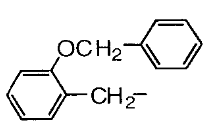
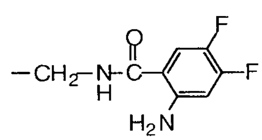
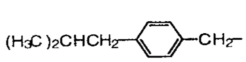
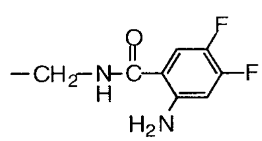
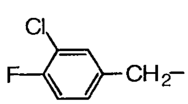
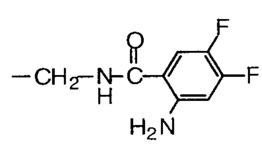
Compd. No.	$R^1R^2>-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
2058		2	2	1	-	H	
2059		2	2	1	-	H	
2060		2	2	1	-	H	
2061		2	2	1	-	H	
2062		2	2	1	-	H	
2063		2	2	1	-	H	
2064		2	2	1	-	H	
2065		2	2	1	-	H	
2066		2	2	1	-	H	
2067		2	2	1	-	H	
2068		2	2	1	-	H	

Table 1.189

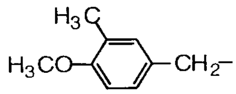
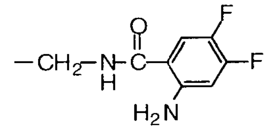
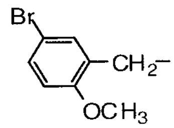
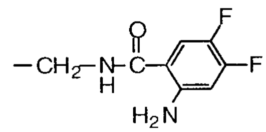
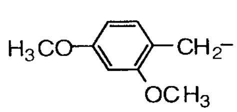
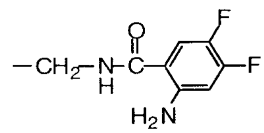
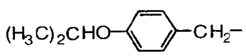
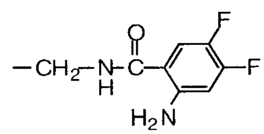
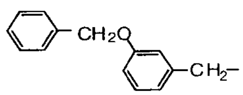
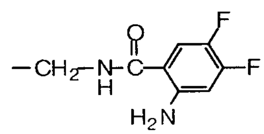
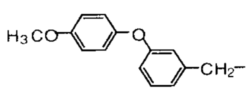
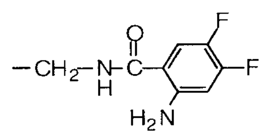
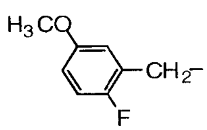
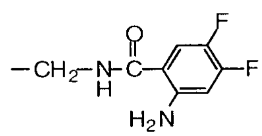
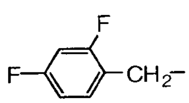
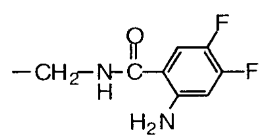
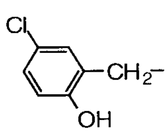
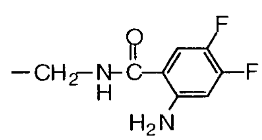
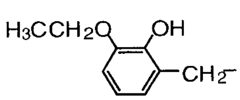
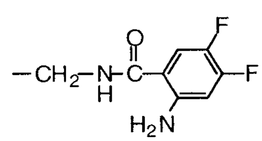
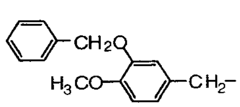
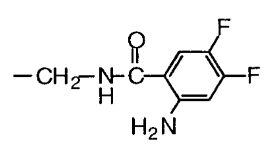
Compd. No.	$R^1R^2>$—$(CH_2)_j$—	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
2069		2	2	1	-	H	
2070		2	2	1	-	H	
2071		2	2	1	-	H	
2072		2	2	1	-	H	
2073		2	2	1	-	H	
2074		2	2	1	-	H	
2075		2	2	1	-	H	
2076		2	2	1	-	H	
2077		2	2	1	-	H	
2078		2	2	1	-	H	
2079		2	2	1	-	H	

Table 1.190

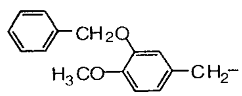
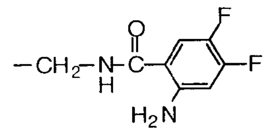
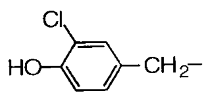
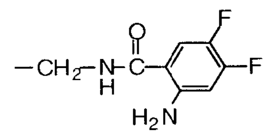
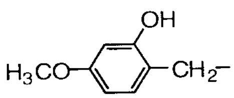
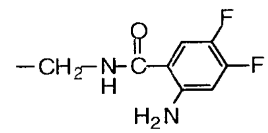
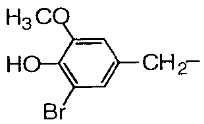
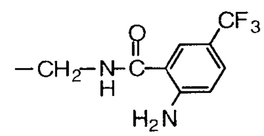
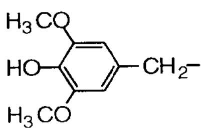
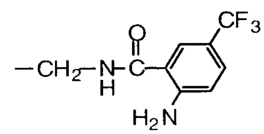
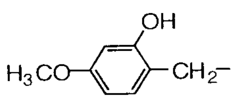
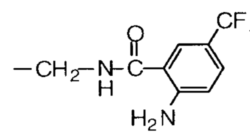
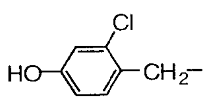
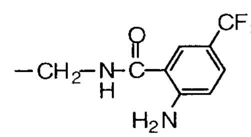
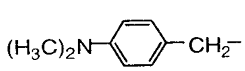
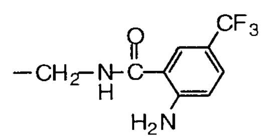
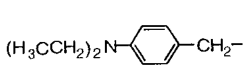
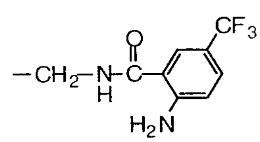
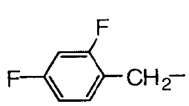
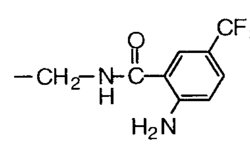
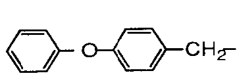
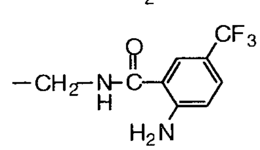
Compd. No.	$R^1R^2>-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
2080		2	2	1	-	H	
2081		2	2	1	-	H	
2082		2	2	1	-	H	
2083		1	2	0	R	H	
2084		1	2	0	R	H	
2085		1	2	0	R	H	
2086		1	2	0	R	H	
2087		1	2	0	R	H	
2088		1	2	0	R	H	
2089		1	2	0	R	H	
2090		1	2	0	R	H	

Table 1.191

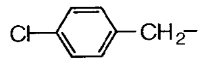
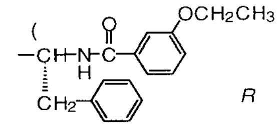
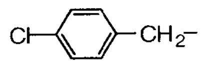
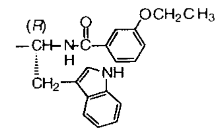
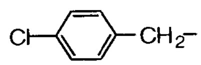
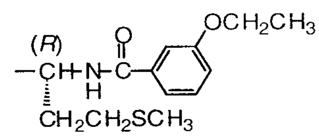
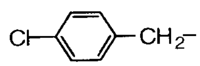
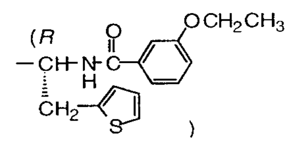
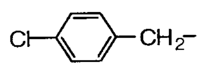
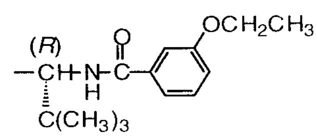
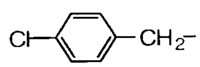
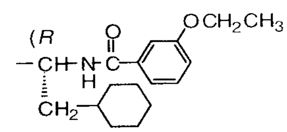
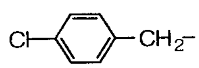
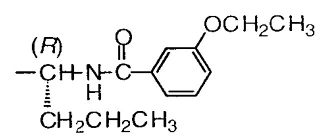
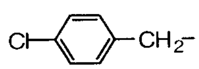
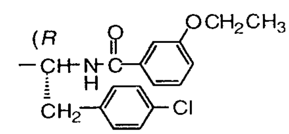
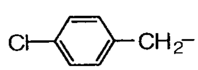
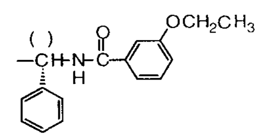
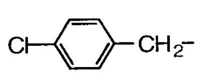
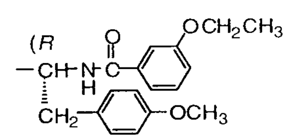
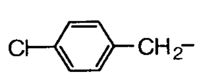
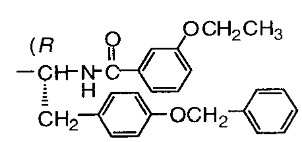
Compd. No.	$\begin{matrix}R^1\\R^2\end{matrix}\!>\!(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
2091		2	2	1	-	H	
2092		2	2	1	-	H	
2093		2	2	1	-	H	
2094		2	2	1	-	H	
2095		2	2	1	-	H	
2096		2	2	1	-	H	
2097		2	2	1	-	H	
2098		2	2	1	-	H	
2099		2	2	1	-	H	
2100		2	2	1	-	H	
2101		2	2	1	-	H	

Table 1.192

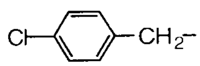
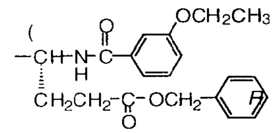
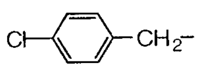
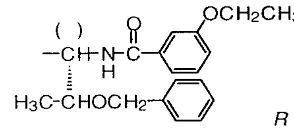
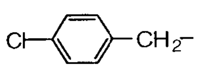
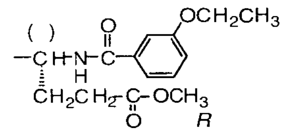
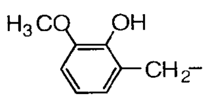
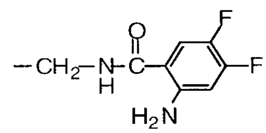
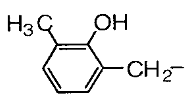
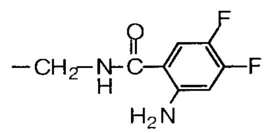
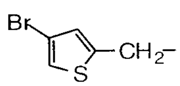
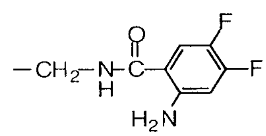
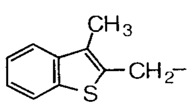
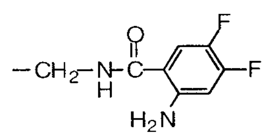
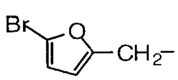
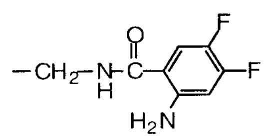
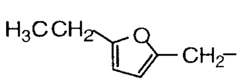
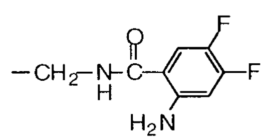
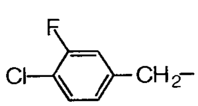
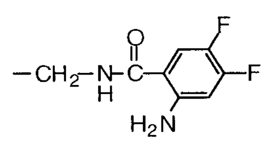
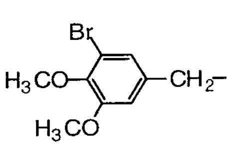
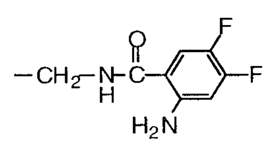
Compd. No.	$R^1R^2>-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
2102		2	2	1	-	H	
2103		2	2	1	-	H	
2104		2	2	1	-	H	
2105		2	2	1	-	H	
2106		2	2	1	-	H	
2107		2	2	1	-	H	
2108		2	2	1	-	H	
2109		2	2	1	-	H	
2110		2	2	1	-	H	
2111		2	2	1	-	H	
2112		2	2	1	-	H	

Table 1.193

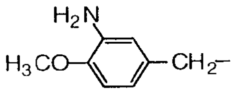
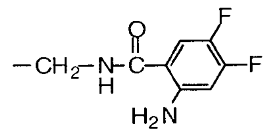
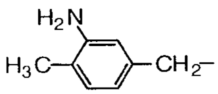
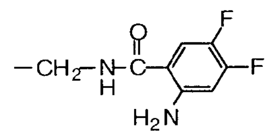
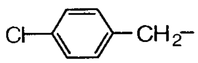
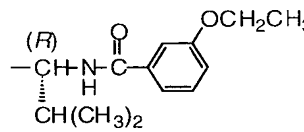
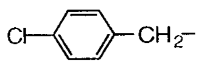
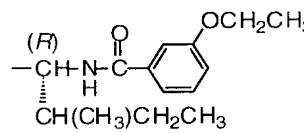
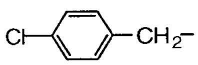
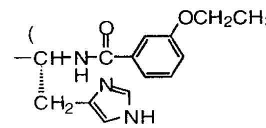
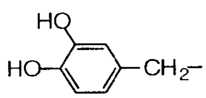
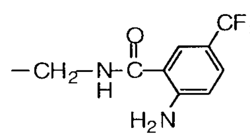
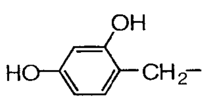
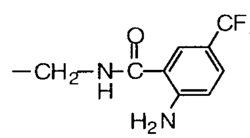
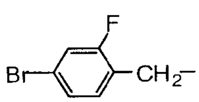
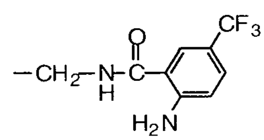
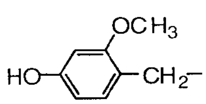
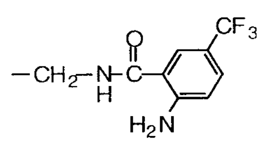
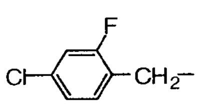
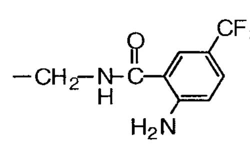
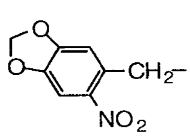
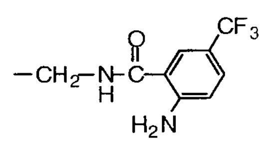
Compd. No.	$R^1R^2>(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
2113		2	2	1	-	H	
2114		2	2	1	-	H	
2115		2	2	1	-	H	
2116		2	2	1	-	H	
2117		2	2	1	-	H	
2118		1	2	0	R	H	
2119		1	2	0	R	H	
2120		1	2	0	R	H	
2121		1	2	0	R	H	
2122		1	2	0	R	H	
2123		1	2	0	R	H	

Table 1.194

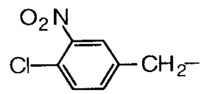
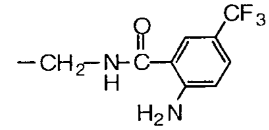
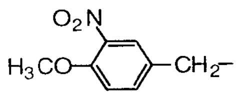
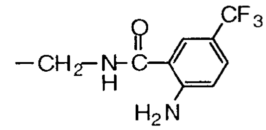
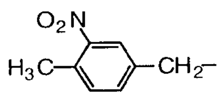
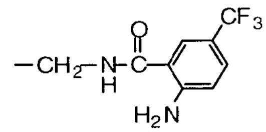
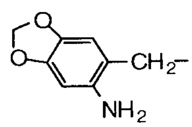
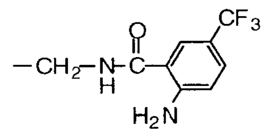
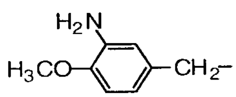
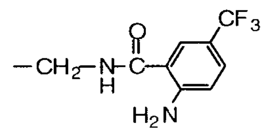
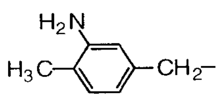
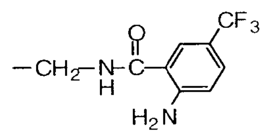
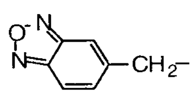
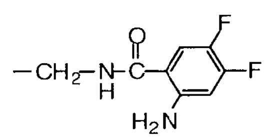
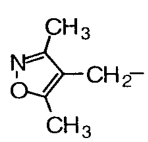
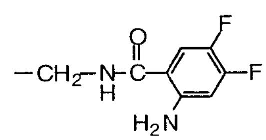
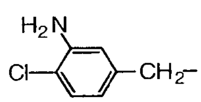
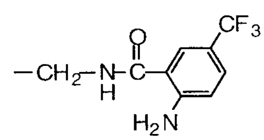
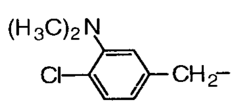
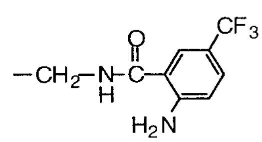
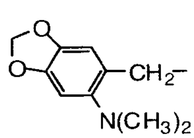
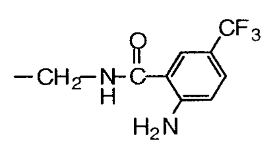
Compd. No.	$R^1R^2>-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
2124		1	2	0	R	H	
2125		1	2	0	R	H	
2126		1	2	0	R	H	
2127		1	2	0	R	H	
2128		1	2	0	R	H	
2129		1	2	0	R	H	
2130		2	2	1	-	H	
2131		2	2	1	-	H	
2132		1	2	0	R	H	
2133		1	2	0	R	H	
2134		1	2	0	R	H	

Table 1.195

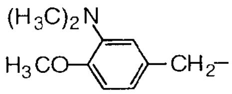
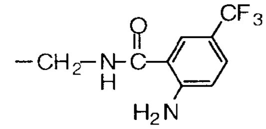
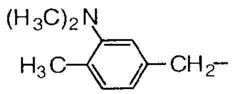
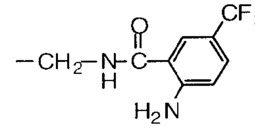
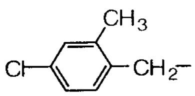
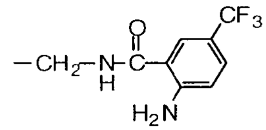
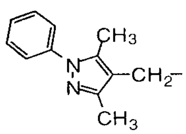
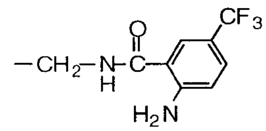
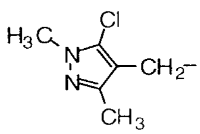
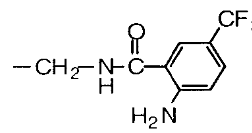
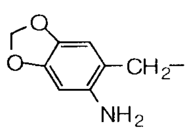
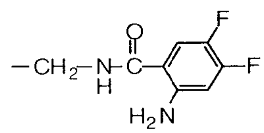
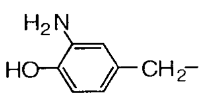
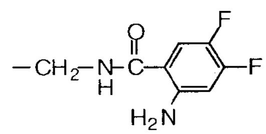
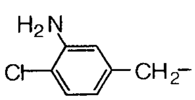
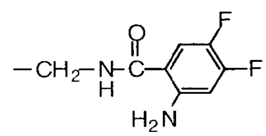
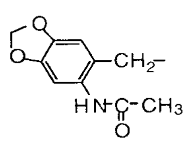
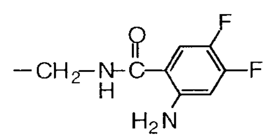
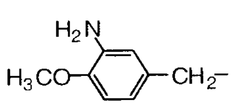
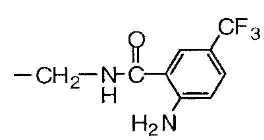
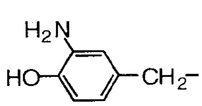
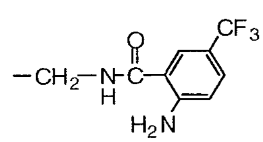
Compd. No.	$R^1R^2>$-$(CH_2)_j$-	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
2135		1	2	0	R	H	
2136		1	2	0	R	H	
2137		1	2	0	R	H	
2138		1	2	0	R	H	
2139		1	2	0	R	H	
2140		2	2	1	-	H	
2141		2	2	1	-	H	
2142		2	2	1	-	H	
2143		2	2	1	-	H	
2144		2	2	1	-	H	
2145		2	2	1	-	H	

Table 1.196

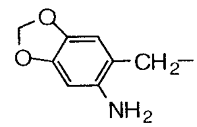
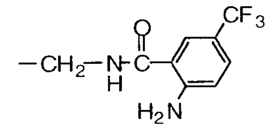
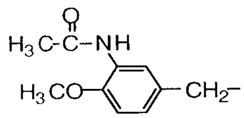
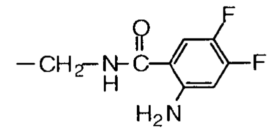
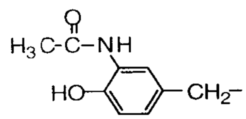
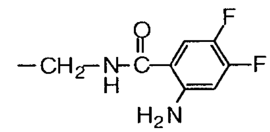
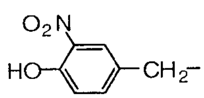
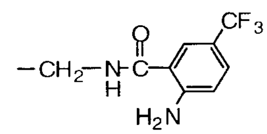
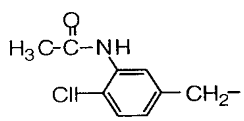
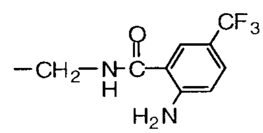
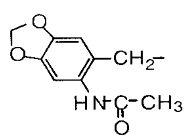
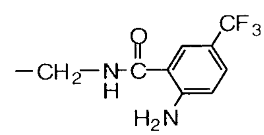
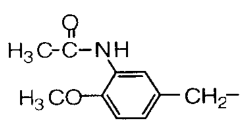
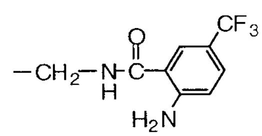
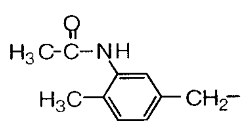
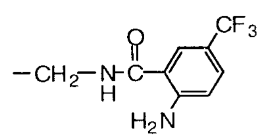
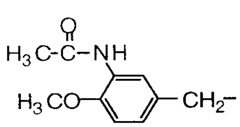
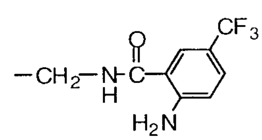
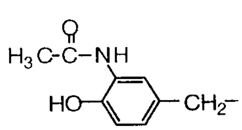
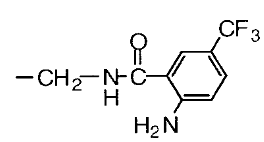
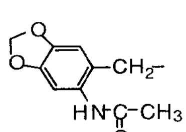
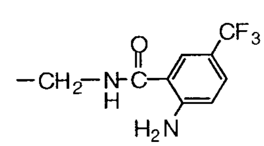
Compd. No.	R^1, R^2 >–$(CH_2)_j$–	k	m	n	chirality	R^3	–$(CH_2)_p$–C(R^4)(R^5)–$(CH_2)_q$–G–R^6
2146		2	2	1	-	H	
2147		2	2	1	-	H	
2148		2	2	1	-	H	
2149		1	2	0	R	H	
2150		1	2	0	R	H	
2151		1	2	0	R	H	
2152		1	2	0	R	H	
2153		1	2	0	R	H	
2154		2	2	1	-	H	
2155		2	2	1	-	H	
2156		2	2	1	-	H	

Table 1.197

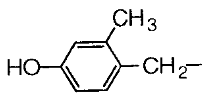
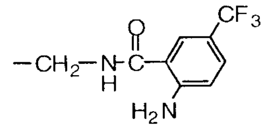
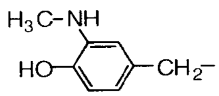
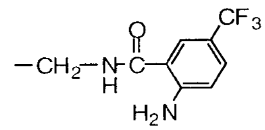
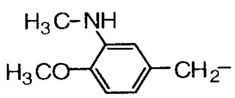
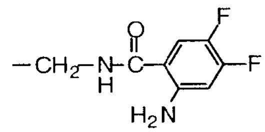
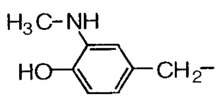
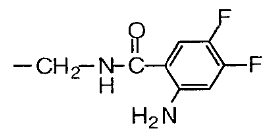
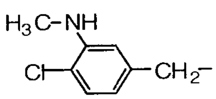
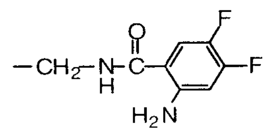
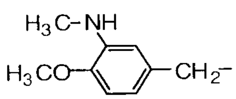
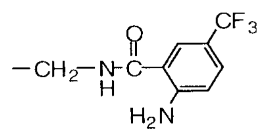
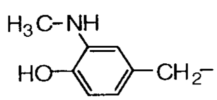
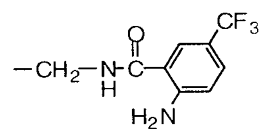
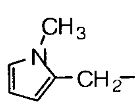
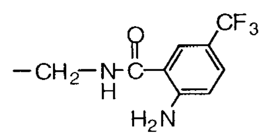
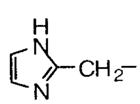
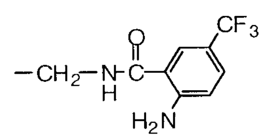
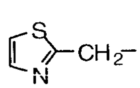
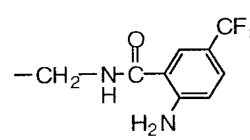
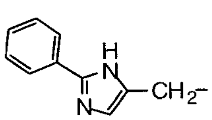
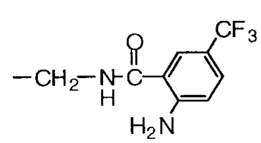
Compd. No.	$R^1R^2{>}(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
2157		1	2	0	R	H	
2158		1	2	0	R	H	
2159		2	2	1	-	H	
2160		2	2	1	-	H	
2161		2	2	1	-	H	
2162		2	2	1	-	H	
2163		2	2	1	-	H	
2164		1	2	0	R	H	
2165		1	2	0	R	H	
2166		1	2	0	R	H	
2167		1	2	0	R	H	

Table 1.198

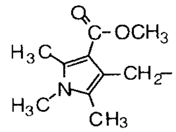
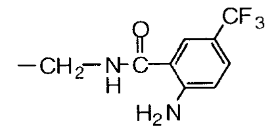
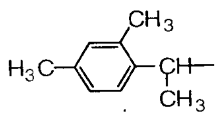
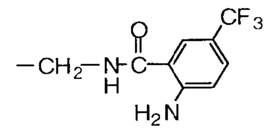
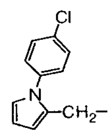
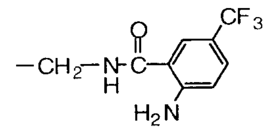
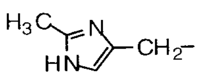
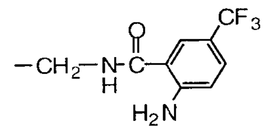
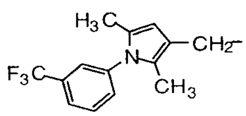
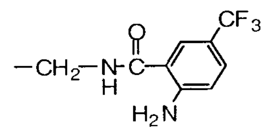
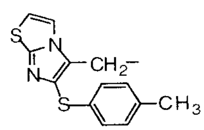
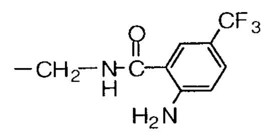
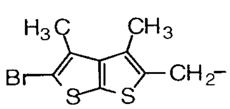
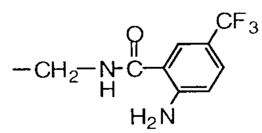
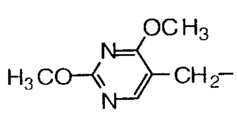
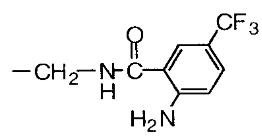
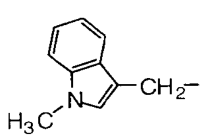
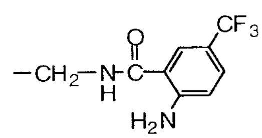
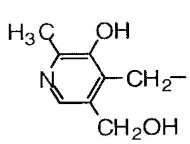
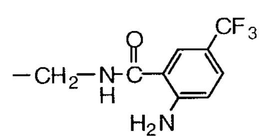
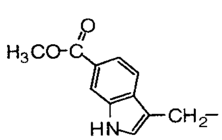
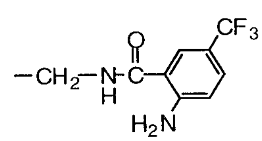
Compd. No.	R^1 R^2 >$-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
2168		1	2	0	R	H	
2169		1	2	0	R	H	
2170		1	2	0	R	H	
2171		1	2	0	R	H	
2172		1	2	0	R	H	
2173		1	2	0	R	H	
2174		1	2	0	R	H	
2175		1	2	0	R	H	
2176		1	2	0	R	H	
2177		1	2	0	R	H	
2178		1	2	0	R	H	

Table 1.199

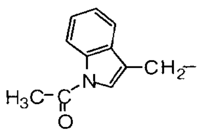
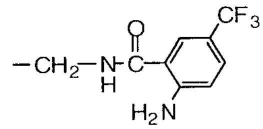
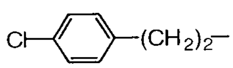
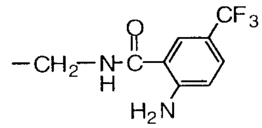
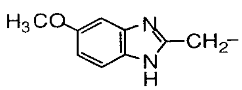
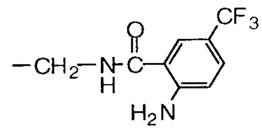
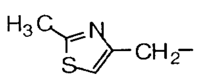
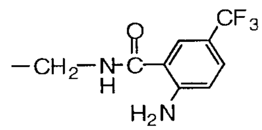
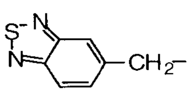
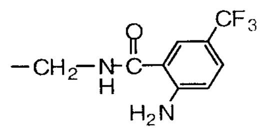
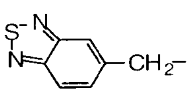
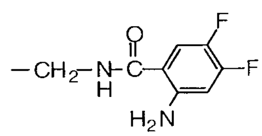
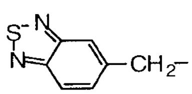
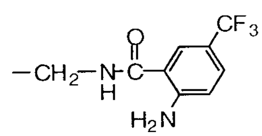
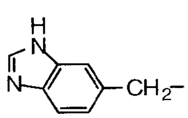
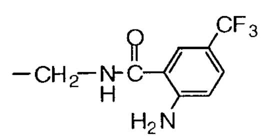
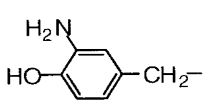
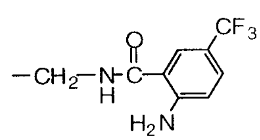
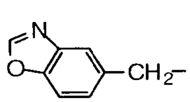
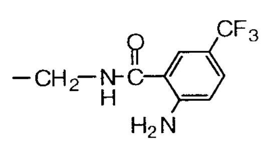
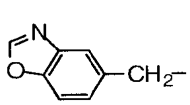
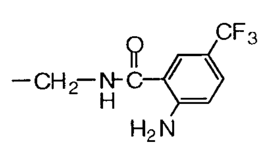
Compd. No.	$R^1R^2CH-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
2179		1	2	0	R	H	
2180		1	2	0	R	H	
2181		1	2	0	R	H	
2182		1	2	0	R	H	
2183		1	2	0	R	H	
2184		2	2	1	-	H	
2185		2	2	1	-	H	
2186		2	2	1	-	H	
2187		1	2	0	R	H	
2188		2	2	1	-	H	
2189		1	2	0	R	H	

Table 1.200

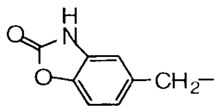
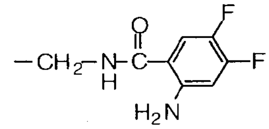
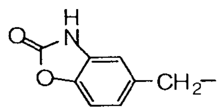
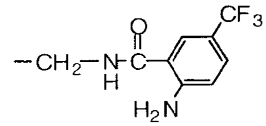
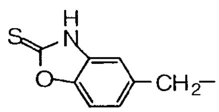
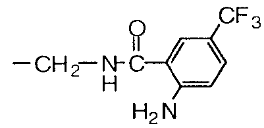
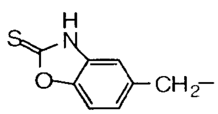
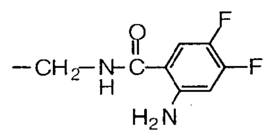
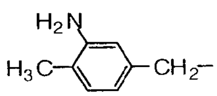
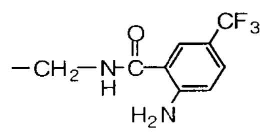
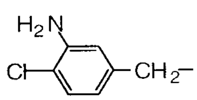
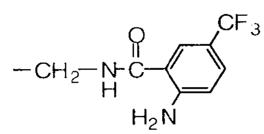
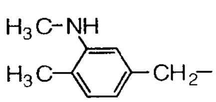
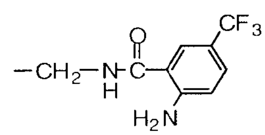
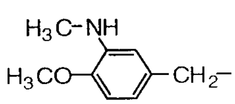
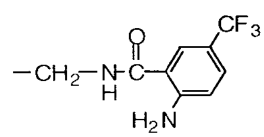
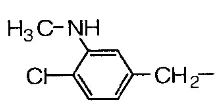
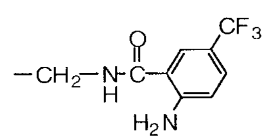
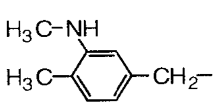
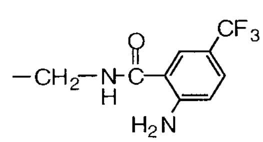
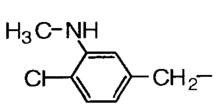
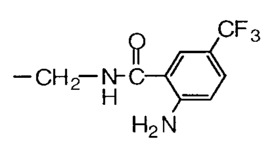
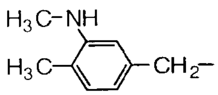
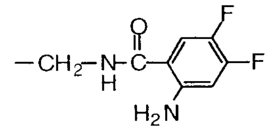
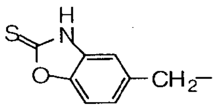
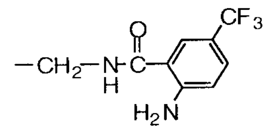
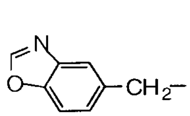
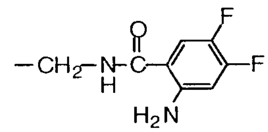
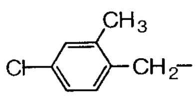
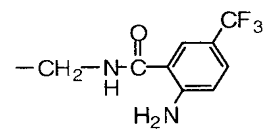
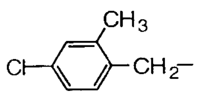
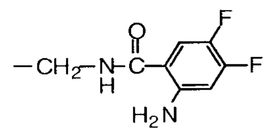
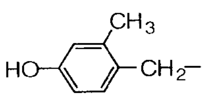
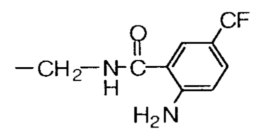
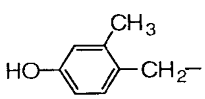
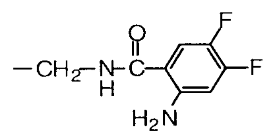
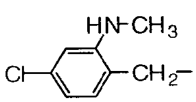
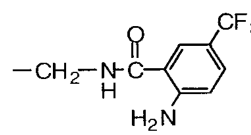
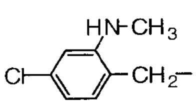
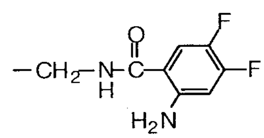
Compd. No.	$R^1R^2>$–$(CH_2)_j$–	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
2190		2	2	1	-	H	
2191		2	2	1	-	H	
2192		2	2	1	-	H	
2193		2	2	1	-	H	
2194		2	2	1	-	H	
2195		2	2	1	-	H	
2196		1	2	0	R	H	
2197		1	2	0	R	H	
2198		1	2	0	R	H	
2199		2	2	1	-	H	
2200		2	2	1	-	H	

Table 1.201

Compd. No.	$R^1R^2>-(CH_2)_j-$	k	m	n	chirality	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
2201		2	2	1	-	H	
2202		1	2	0	R	H	
2203		2	2	1	-	H	
2204		2	2	1	-	H	
2205		2	2	1	-	H	
2206		2	2	1	-	H	
2207		2	2	1	-	H	
2208		2	2	1	-	H	
2209		2	2	1	-	H	

The present invention can also use acid addition salt of the cyclic amine compound where such acids include, for example, mineral acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, carbonic acid, and the like, as well as organic acids such as maleic acid, citric acid, malic acid, tartaric acid, fumaric acid, methanesulfonic acid, trifluoroacetic acid, formic acid, and the like.

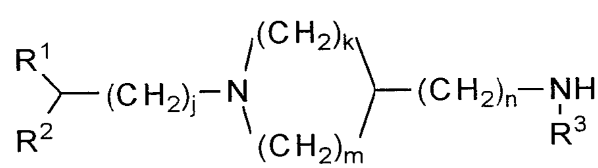
Furthermore, the present invention can also use a C_1-C_6 alkyl addition salt of the cyclic amine compound, such as 1-(4-chlorobenzyl)-1-methyl-4-[{*N*-(3-trifluoromethylbenzoyl)glycyl}aminomethyl]piperidinium iodide, where such alkyl include, for example, a methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, isopropyl, isobutyl, *sec*-butyl, *tert*-butyl, isopentyl, neopentyl, *tert*-pentyl, 2-methylpentyl, 1-ethylbutyl, and the like, suitably specifically including, a methyl and ethyl group. As preferred specific examples for counter anion of the ammonium cation, a halide anion such as fluoride, chloride, bromide or iodide can be listed.

The present invention may use racemates and all possible optically active forms of the compound represented by the above formula (I).

Compound represented by the above general formula (I) can be synthesized by any of the general preparations given below.

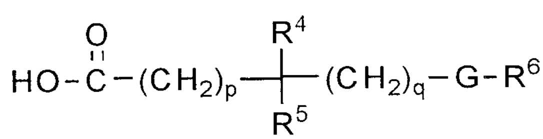
(Preparation 1)

A preparation which call for treating one equivalent of a compound represented by the formula (II) below:



(II)

{where R^1, R^2, R^3, j, k, m, and n are the same as defined respectively in the above formula (I)} with 0.1-10 equivalents of a carboxylic acid represented by the formula (III) below:



(III)

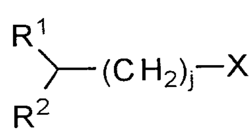
{where R^4, R^5, R^6, G, p, and q are the same as defined respectively in the above formula (I)}, or its reactive derivative, either in the absence or presence of solvent.

The reactive derivative for the carboxylic acid in the above formula (III) include highly reactive carboxylic acid derivatives, which are usually used in synthetic organic chemistry, such as acid halides, acid anhydrides, mixed acid anhydrides.

Such reactions can be more smoothly run by using suitable amounts of a dehydrating agent such as molecular sieve, coupling reagent such as dicyclohexylcarbodiimide (DCC), *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide (EDCI or WSC), carbonyldiimidazole (CDI), *N*-hydroxysuccinimide (HOSu), *N*-hydroxybenzotriazole (HOBt), benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP®), 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), 2-(5-norbornene-2,3-dicarboxyimido)-1,1,3,3-tetramethyluronium tetrafluoroborate (TNTU), *O*-(*N*-succinimidyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TSTU), bromotris(pyrrolidino)phosphonium hexafluorophosphate (PyBroP®), and the like, or base including inorganic salts such as potassium carbonate, sodium carbonate, sodium hydrogencarbonate, and the like, amines such as triethylamine, diisopropylethylamine, and pyridine, and the like, or polymer supported bases such as (piperidinomethyl)polystyrene, (morpholinomethyl)polystyrene, (diethylaminomethyl)polystyrene, poly(4-vinylpyridine), and the like.

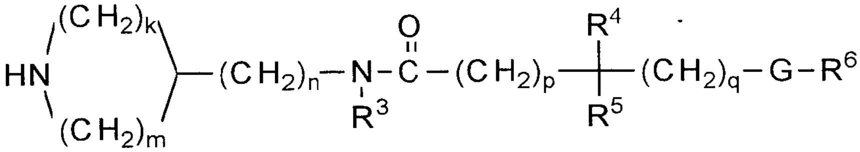
(Preparation 2)

A preparation which calls for treating 1 equivalent of an alkylating reagent given by the formula (IV) below:



(IV)

{where R^1, R^2, and j are the same as defined respectively in the above formula (I)}; X represents a halogen atom, alkylsulfonyloxy group, or arylsulfonyloxy group}, with 0.1-10 equivalents of a compound represented by the formula (V) below:



(V)

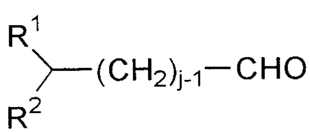
{where R^3, R^4, R^5, R^6, G, k, m, n, p, and q are the same as defined respectively in the above formula (I)} either in the absence or presence of solvent.

Such reactions can be more smoothly run if a base similar to that used in the above preparation 1 is present. In addition, the reactions in these preparations can also be promoted by iodide such as potassium iodide, sodium iodide, and the like.

In the above formulas (IV), X represents a halogen atom, alkylsulfonyloxy group, arylsulfonyloxy group. Such halogen atoms include preferably chlorine, bromine, and iodine atoms. Suitable specific examples for the alkylsulfonyloxy groups include methylsulfonyloxy, trifluoromethylsulfonyloxy group, and the like. A preferred specific example for the arylsulfonyloxy group includes a tosyloxy group.

(Preparation 3)

A preparation which calls for treating 1 equivalent of an aldehyde represented by the formula (VI) below:



(VI)

{where R^1 and R^2 are the same as defined respectively in the above formula (I); j represents 1 or 2} or the formula (VII) below:

R^1-CHO (VII)

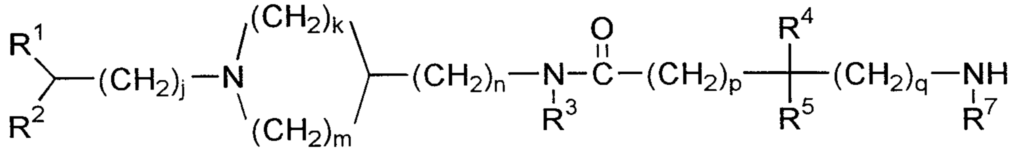
{where R^1 is the same as defined in the above formula (I); j represents 0}, with 0.1-10 equivalents of a compound represented by the formula (V) either in the absence or presence of solvent under reductive conditions.

Such reactions are in general called reductive amination reactions and such reductive conditions may be generated by catalytic hydrogenation using a catalyst containing a metal such as palladium, platinum, nickel, rhodium, or the like, using complex hydrides, such as lithium aluminum hydride, sodium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride, and the

like, boranes, or electrolytic reduction, and the like.

(Preparation 4)

A preparation which call for treating one equivalent of a compound represented by the formula (VIII) below:


(VIII)

{where R^1, R^2, R^3, R^4, R^5, R^7, j, k, m, n, p and q are the same as defined respectively in the above formula (I)} with 0.1-10 equivalents of a carboxylic acid or sulfonic acid represented by the formula (IX) below:

$$HO\text{-}A\text{-}R^6 \qquad (IX)$$

{where R^6 is the same as defined in the above formulas (I); "A" represents a carbonyl group or sulfonyl group}, or its reactive derivative, either in the absence or presence of solvent.

The reactive derivative for the carboxylic acid or sulfonic acid in the above formula (IX) include highly reactive carboxylic acid or sulfonic acid derivative, which are usually used in synthetic organic chemistry, such as acid halides, acid anhydrides, mixed acid anhydrides.

Such reactions can be more smoothly run by using suitable amounts of a dehydrating agent, coupling reagent, or base which are similar to those used in the above preparation 1.

(Preparation 5)

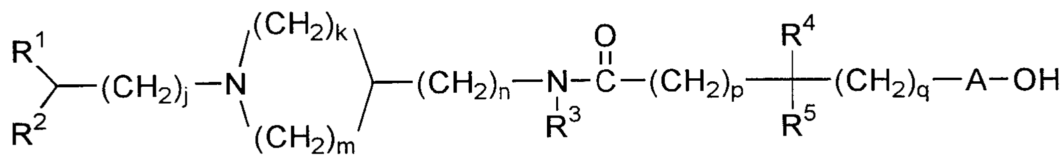
A preparation which calls for treating 1 equivalent of a compound represented by the above formula (VIII) with 0.1-10 equivalents of a isocyanate or isothiocyanate represented by the formula (X) below:

$$Z{=}C{=}N\text{-}R^6 \qquad (X)$$

{where R^6 is the same as defined in the above formulas (I)}; Z represents a oxygen atom or sulfur atom}, either in the absence or presence of solvent.

(Preparation 6)

A preparation which calls for treating 1 equivalent of a compound represented by the formula (XI) below:



(XI)

{where R^1, R^2, R^3, R^4, R^5, j, k, m, n, p and q are the same as defined respectively in the above formula (I)}; "A" represents a carbonyl group or sulfonyl group} with 0.1-10 equivalents of an amine represented by the formula (XII) below:

$$R^6\text{-}NH_2 \qquad \text{(XII)}$$

{where R^6 is the same as defined in the above formula (I)}, either in the absence or the presence of solvent.

Such reactions can be more smoothly run by using suitable amounts of a dehydrating agent, coupling reagent, or base which are similar to those used in the above preparation 1.

If the substrates submitted to each of the above preparations contains a substituent which reacts under each reaction condition or is thought to adversely affect the reaction in general in synthetic organic chemistry, that functional group can be protected by a known suitable protecting group followed by the reaction of the above preparations and deprotection using a known procedure to obtain the desired compound.

Furthermore, a compound of the present invention can be prepared by the further conversion of the substituent(s) of the compound, prepared with the above preparations 1-6, using known reactions which are usually used in synthetic organic chemistry, such as alkylation, acylation, reduction, and so on.

Each of the above preparations may use solvents for the reaction such as halogenated hydrocarbons such as dichloromethane, chloroform, and the like, aromatic hydrocarbons such as benzene, toluene, and the like, ethers such as diethyl ether, tetrahydrofuran, and the like, esters such as ethyl acetate, aprotic polar solvents such as dimethylformamide, dimethyl sulfoxide, acetonitrile, and the like, alcohols such as methanol, ethanol, isopropyl alcohol, and the like.

The reaction temperature in either of the preparations should be in the range of -78 °C - +150 °C, preferably 0 °C - 100 °C. After completion of the reaction, the usual isolation and purification operations such as concentration, filtration, extraction, solid-phase extraction, recrystallization, chromatography, and the like may be used, to isolate the desired cyclic amine compound represented by the above formula (I). These can be converted into pharmaceutically acceptable acid addition salt or C_1-C_6 alkyl addition salt by the usual method.

Potential Industrial Utilities

The chemokine receptor antagonist, which contain the cyclic amine compound, its pharmaceutically acceptable acid addition salt or a pharmaceutically acceptable C_1-C_6 alkyl addition salt of this invention, which inhibits chemokines such as MIP-1α and/or MCP-1 and the like from action on target cells, are useful as therapeutic agents and/or preventive preparation for diseases such as atherosclerosis, rheumatoid arthritis, psoriasis, asthma, ulcerative colitis, nephritis (nephropathy), multiple sclerosis, pulmonary fibrosis, myocarditis, hepatitis, pancreatitis, sarcoidosis, Crohn's disease, endometriosis, congestive heart failure, viral meningitis, cerebral infarction, neuropathy, Kawasaki disease, sepsis, and the like, in which tissue infiltration of blood monocytes, lymphocytes, and the like plays a major role in the initiation, progression, and maintenance of the disease.

Examples

The present invention is now specifically described by the following examples. However, the present invention is not limited to these compounds described in these examples. Compound numbers in these examples represent numbers attached to these compounds listed as suitable specific examples in Tables 1.1—1.201.

Reference Example 1: Preparation of 3-Amino-1-(4-chlorobenzyl)pyrrolidine dihydrochloride.

4-Chlorobenzyl chloride (4.15 g, 25.8 mmol) and $^{i}Pr_2NEt$ (6.67 g, 51.6 mmol) were added to a solution of 3-{(*tert*-butoxycarbonyl)amino}pyrrolidine (4.81 g, 25.8 mmol) in DMF (50 mL). The reaction mixture was stirred at 70 °C for 15 h and the solvent was removed under reduced pressure. Recrystallization (CH_3CN, 50 mL) provided the desired material, 3-(*tert*-butoxycarbonyl)amino-1-(4-chlorobenzyl)pyrrolidine as a pale yellow solid (6.43 g, 80.2%): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.37 (s, 9 H), 1.5-1.7 (br, 1 H), 2.1-2.4 (m, 2 H), 2.5-2.7 (m, 2 H), 2.83 (br, 1 H), 3.57 (s, 2 H), 4.1-4.3 (br, 1 H), 4.9-5.1 (br, 1 H), 7.15-7.35 (br, 4 H); The purity was determined by RPLC/MS (98%); ESI/MS m/e 311.0 (M^++H, $C_{16}H_{24}ClN_2O_2$).

A solution of 3-(*tert*-butoxycarbonyl)amino-1-(4-chlorobenzyl)pyrrolidine (6.38 g, 20.5 mmol) in CH_3OH (80 mL) was treated with 1 N HCl-Et_2O (100 mL) and was stirred at 25 °C for 15 h. The solvent was removed under reduced pressure to afford a solid which was purified by recrystallization (1:2 CH_3OH-CH_3CN, 150 mL) to give 3-amino-1-(4-chlorobenzyl)pyrrolidine dihydrochloride as a white powder (4.939 g, 84.9%): ^1H NMR (d_6-DMSO, 300 MHz) δ 3.15 (br, 1 H), 3.3-3.75 (br-m, 4 H), 3.9 (br, 1 H), 4.05 (br, 1 H), 4.44 (br, 1 H), 4.54 (br, 1 H), 7.5-7.7 (m, 4 H), 8.45 (br, 1 H), 8.60 (br, 1 H); The purity was determined by RPLC/MS (>99%); ESI/MS m/e 211.0 (M^++H, $C_{11}H_{16}ClN_2$).

Optically active (*R*)-3-amino-1-(4-chlorobenzyl)pyrrolidine dihydrochloride and (*S*)-3-amino-1-(4-chlorobenzyl)pyrrolidine dihydrochloride were also prepared pursuant to the above method using the corresponding reactant respectively. The products showed the same ^1H NMR with that of the racemate.

Example 1: Preparation of 3-(*N*-Benzoylglycyl)amino-1-(4-chlorobenzyl)pyrrolidine (Compound No. 1).

N-Benzoylglycine (9.9 mg, 0.055 mmol), 3-ethyl-1-{3-(dimethylaminopropyl}carbodiimide hydrochloride (EDCI) (10.5 mg) and 1-

hydroxybenzotriazole hydrate (HOBt) (7.4 mg) were added to a solution of 3-amino-1-(4-chlorobenzyl)pyrrolidine dihydrochloride (14.2 mg, 0.050 mmol) and Et_3N (15.2 mg) in $CHCl_3$ (2.5 mL). The reaction mixture was stirred at 25 °C for 16 h, washed with 2 N aqueous NaOH (2 mL x 2) and brine (1 mL). After filtration through a PTFE membrane filter, the solvent was removed under reduced pressure to afford 3-(*N*-benzoylglycyl)amino-1-(4-chlorobenzyl)pyrrolidine (compound No. **1**) as a pale yellow oil (17.7 mg, 95%): The purity was determined by RPLC/MS (95%); ESI/MS m/e 372.0 (M^++H, $C_{20}H_{22}ClN_3O_2$).

Examples 2-32.

The compounds of this invention were synthesized pursuant to methods of Example 1 using the corresponding reactant respectively. The ESI/MS data and yields are summarized in Table 2.

Table 2

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 2	2	C21 H24 Cl N3 O2	386	16.4	85
Example 3	3	C19 H21 Cl N4 O2	373	18.7	100
Example 4	4	C21 H21 Cl F3 N3 O2	440	57.2	69
Example 5	82	C22 H23 Cl F3 N3 O2	454	5.6	11
Example 6	85	C21 H24 Cl N3 O2	386	22.6	59
Example 7	86	C21 H23 Cl N4 O4	431	21.2	98
Example 8	214	C22 H25 Cl N2 O2	385	23.9	62
Example 9	215	C23 H27 Cl N2 O3	415	17.4	84
Example 10	216	C20 H23 Cl N2 O2 S	391	21.6	quant
Example 11	217	C23 H27 Cl N2 O4	431	15.3	66
Example 12	218	C23 H27 Cl N2 O2	399	12.8	64
Example 13	219	C22 H24 Cl F N2 O3	419	18.1	86
Example 14	220	C22 H25 Cl N2 O2	385	16.4	85
Example 15	221	C21 H23 Cl N2 O2	371	14.9	80
Example 16	222	C21 H22 Cl2 N2 O2	405	13.3	65
Example 17	223	C25 H31 Cl N2 O3	443	18.4*	63
Example 18	224	C20 H23 Cl N2 O3 S	407	11.2	28
Example 19	225	C22 H26 Cl N3 O2	400	22.7	quant
Example 20	226	C23 H28 Cl N3 O3	430	21.0	98
Example 21	227	C22 H25 Cl2 N3 O2	434	21.9	100
Example 22	228	C23 H28 Cl N3 O3	430	20.8	97

Example 23	229	C25 H32 Cl N3 O2	462	25.4	quant
Example 24	230	C26 H31 Cl F N3 O2	472	26.0	quant
Example 25	231	C24 H28 Cl N3 O3	442	30.3*	quant
Example 26	232	C22 H32 Cl N3 O2	406	3.9	19
Example 27	233	C23 H28 Cl N3 O2	414	8.5	41
Example 28	234	C22 H27 Cl N4 O2	415	7.3	35
Example 29	235	C24 H29 Cl2 N3 O2	462	9.0	39
Example 30	236	C25 H29 Cl N4 O3 S	501	17.4	69
Example 31	237	C21 H24 Cl N3 O3	402	14.2	71
Example 32	238	C21 H23 Cl2 N3 O3	436	23.4	quant

*Yield of TFA salt.

Reference Example 2: Preparation of (*R*)-3-{*N*-(*tert*-Butoxycarbonyl)glycyl}amino-1-(4-chlorobenzyl)pyrrolidine.

A mixture of (*R*)-3-amino-1-(4-chlorobenzyl)pyrrolidine dihydrochloride (4.54 g, 16.0 mmol), 2 N NaOH solution (80 mL), and ethyl acetate (80 mL) was shaken, the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (80 mL x 2). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and evaporated to give free (*R*)-3-amino-1-(4-chlorobenzyl)pyrrolidine (3.35 g, 99%).

A solution of (*R*)-3-amino-1-(4-chlorobenzyl)pyrrolidine (3.35 g, 16 mmol) in CH_2Cl_2 (80 mL) was treated with Et_3N (2.5 mL, 17.6 mmol), *N*-*tert*-butoxycarbonylglycine (2.79 g, 16.0 mmol), EDCI (3.07 g, 16.0 mmol) and HOBt (2.16 g, 16 mmol). After the reaction mixture was stirred at 25 °C for 16 h, 2 N NaOH solution (80 mL) was added. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (100 mL x 3). The combined organic layer was washed with water (100 mL x 2) and brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography (SiO_2, ethyl acetate) afforded the desired (*R*)-3-{*N*-(*tert*-butoxycarbonyl)glycyl}amino-1-(4-chlorobenzyl)pyrrolidine (5.40 g, 92%).

Reference Example 3: Preparation of (R)-1-(4-Chlorobenzyl)-3-(glycylamino)pyrrolidine.

To a solution of (*R*)-3-{*N*-(*tert*-butoxycarbonyl)glycyl}amino-1-(4-chlorobenzyl)pyrrolidine (5.39 g, 14.7 mmol) in methanol (60 mL) was added 4 N HCl in dioxane (38 mL). The solution was stirred at room temperature for 2 h. The reaction mixture was concentrated and 2 N NaOH solution (80 mL) was added. The mixture was extracted with dichloromethane (80 mL x 3), and the combined

extracts were dried over sodium sulfate and concentrated. Column chromatography (SiO_2, AcOEt/EtOH/Et_3N = 90/5/5) gave (*R*)-3-(glycyl)amino-1-(4-chlorobenzyl)pyrrolidine (3.374 g, 86%): ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.77 (dd, J = 1.3 and 6.9 Hz, 1 H), 2.20-3.39 (m, 2 H), 2.53 (dd, J = 3.3 and 9.6 Hz, 1 H), 2.62 (dd, J = 6.6 and 9.6 Hz, 1 H), 2.78-2.87 (m, 1 H), 3.31 (s, 2 H), 3.57 (s, 2 H), 4.38-4.53 (br, 1 H), 7.18-7.32 (m, 4 H), 7.39 (br. s, 1 H).

Other 3-acylamino-1-(4-chlorobenzyl)pyrrolidines were also synthesized pursuant to methods of Reference Example 2 and 3 using the corresponding reactants respectively.

(*S*)-1-(4-Chlorobenzyl)-3-(glycylamino)pyrrolidine: 3.45 g, 79% (2 steps).

(*R*)-3-(β-Alanylamino)-1-(4-chlorobenzyl)pyrrolidine: 3.79 g, 85% (2 steps).

(*S*)-3-(β-Alanylamino-)1-(4-chlorobenzyl)pyrrolidine: 3.72 g, 86% (2 steps).

(*R*)-3-{(*S*)-Alanylamino}-1-(4-chlorobenzyl)pyrrolidine: 368 mg, 65% (2 steps).

(*R*)-3-{(*R*)-Alanylamino}-1-(4-chlorobenzyl)pyrrolidine: 425 mg, 75% (2 steps).

(*R*)-3-{(2*S*)-2-Amino-3-thienylpropanoyl}amino-1-(4-chlorobenzyl)pyrrolidine: 566 mg, 78% (2 steps).

(*R*)-3-{(2*R*)-2-Amino-3-thienylpropanoyl}amino-1-(4-chlorobenzyl)pyrrolidine: 585 mg, 81% (2 steps).

(*R*)-3-(2-Amino-2-methylpropanoyl)amino-1-(4-chlorobenzyl)pyrrolidine: 404 mg, 66% (2 steps).

(*R*)-3-{(2*S*)-2-Amino-4-(methylsulfonyl)butanoyl}amino-1-(4-chlorobenzyl)pyrrolidine: 535 mg, 72% (2 steps).

Furthermore (*R*)-3-(glycylamino)-1-(4-methylbenzyl)pyrrolidine, (*R*)-1-(4-bromobenzyl)-3-(glycylamino)pyrrolidine, (*R*)-1-(2,4-dimethylbenzyl)-3-(glycylamino)pyrrolidine, and (*R*)-1-(3,5-dimethylisoxazol-4-ylmethyl)-3-(glycylamino)pyrrolidine were also synthesized pursuant to methods of Reference Example 1, 2 and 3 using the corresponding reactants respectively.

(*R*)-3-(Glycylamino)-1-(4-methylbenzyl)pyrrolidine: 4.65 g, 62% yield from 3-{(*tert*-butoxycarbonyl)amino}pyrrolidine.

(*R*)-1-(4-Bromobenzyl)-3-(glycylamino)pyrrolidine: 2.55 g, 68% yield from (*R*)-3-amino-1-(4-bromobenzyl)pyrrolidine; ^{1}H NMR ($CDCl_3$, 270 MHz) δ

1.37-1.78 (m, 3 H), 2.23-2.39 (m, 2 H), 2.50-2.67 (m, 2 H), 2.80-2.89 (m, 1 H), 3.32 (s, 2 H), 3.58 (s, 2 H), 4.39-4.55 (m, 1 H), 7.21 (d, J = 6.5 Hz, 2 H), 7.45 (d, J = 6.5 Hz, 2 H).

(*R*)-1-(2,4-Dimethylbenzyl)-3-(glycylamino)pyrrolidine: 1.56 g, 58% yield from 3-{(*tert*-butoxycarbonyl)amino}pyrrolidine; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.55-1.78 (m, 3 H), 2.30(s, 3 H), 2.23-2.31 (m, 2 H), 2.33(s, 3 H), 2.51-2.63 (m, 2 H), 2.78-2.87 (m, 1 H), 3.30 (s, 2 H), 3.55 (s, 2 H), 4.38-4.60 (m, 1 H), 6.95 (d, J = 7.6 Hz, 1 H), 6.97 (s, 1 H), 7.13 (d, J = 7.6 Hz, 1 H), 7.43 (br-s, 1 H).

(*R*)-1-(3,5-Dimethylisoxazol-4-ylmethyl)-3-(glycylamino)pyrrolidine: 3.14 g, 45% yield from 3-{(*tert*-butoxycarbonyl)amino}pyrrolidine.

Example 33: Preparation of (*S*)-3-[*N*-{3,5-Bis(trifluoromethyl)benzoyl}glycyl]amino-1-(4-chlorobenzyl)pyrrolidine (Compound No. 5).

A solution of 3,5-bis(trifluoromethyl)benzoyl chloride (0.060 mmol) in chloroform (0.4 mL) was added to a solution of (*S*)-1-(4-chlorobenzyl)-3-(glycylamino)pyrrolidine (0.050 mmol) and triethylamine (0.070 mmol) in chloroform (1.0 mL). After the reaction mixture was agitated at room temperature for 2.5 h, (aminomethyl)polystyrene resin (1.04 mmol/g, 50 mg, 50 mmol) was added and the mixture was agitated at room temperature for 12 h. The reaction mixture was filtered and the resin was washed with dichloromethane (0.5 mL). The filtrate and washing were combined, dichloromethane (4 mL) was added, and the solution was washed with 2 N aqueous NaOH solution (0.5 mL) to give (*S*)-3-[*N*-{3,5-bis(trifluoromethyl)benzoyl}glycyl]amino-1-(4-chlorobenzyl)pyrrolidine (compound No. **5**) (14.4 mg, 57%): The purity was determined by RPLC/MS (97%); ESI/MS m/e 508.0 (M^++H, $C_{22}H_{20}ClF_6N_3O_2$).

Examples 34-239.

The compounds of this invention were synthesized pursuant to methods of Example 33 using the corresponding reactant respectively. The ESI/MS data and yields are summarized in Table 3.

Table 3

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 34	5	$C_{22}H_{20}ClF_6N_3O_2$	508.0	14.4	57

Example 35	6	$C_{21}H_{21}ClF_3N_3O_2$	440.0	17.0	77
Example 36	7	$C_{20}H_{21}BrClN_3O_2$	450.0	17.7	79
Example 37	8	$C_{20}H_{21}ClFN_3O_2$	390.0	12.7	65
Example 38	9	$C_{20}H_{20}Cl_3N_3O_2$	440.0	39.0	quant
Example 39	10	$C_{21}H_{24}ClN_3O_3$	402.5	23.5	quant
Example 40	11	$C_{22}H_{26}ClN_3O_4$	432.5	22.4	quant
Example 41	12	$C_{22}H_{26}ClN_3O_4$	432.5	15.9	74
Example 42	13	$C_{21}H_{21}ClF_3N_3O_2$	440.0	13.1	60
Example 43	14	$C_{21}H_{24}ClN_3O_2$	386.0	16.4	85
Example 44	15	$C_{20}H_{21}Cl_2N_3O_2$	406.0	15.7	77
Example 45	16	$C_{21}H_{24}ClN_3O_2$	402.0	28.2	quant
Example 46	17	$C_{20}H_{20}Cl_3N_3O_2$	442.0	35.6	quant
Example 47	18	$C_{21}H_{21}ClN_4O_2$	397.5	22.8	quant
Example 48	19	$C_{21}H_{22}ClN_3O_4$	416.0	16.3	78
Example 49	20	$C_{21}H_{20}ClF_4N_3O_2$	458.0	24.9	quant
Example 50	21	$C_{21}H_{20}ClF_4N_3O_2$	458.0	17.9	78
Example 51	22	$C_{21}H_{20}ClF_4N_3O_2$	458.0	9.4	41
Example 52	23	$C_{21}H_{20}ClF_4N_3O_2$	458.0	15.4	67
Example 53	24	$C_{21}H_{21}ClF_3N_3O_3$	456.0	20.7	91
Example 54	25	$C_{21}H_{20}ClF_4N_3O_2$	458.0	18.5	81
Example 55	26	$C_{20}H_{21}ClN_4O_4$	417.0	21.9	quant
Example 56	27	$C_{20}H_{21}ClN_4O_4$	417.0	16.8	81
Example 57	28	$C_{20}H_{21}ClN_4O_4$	417.0	6.8	33
Example 58	29	$C_{22}H_{20}ClF_6N_3O_2$	508.0	20.8	82
Example 59	30	$C_{21}H_{21}ClF_3N_3O_2$	440.0	15.2	69
Example 60	31	$C_{20}H_{21}BrClN_3O_2$	450.0	15.6	69
Example 61	32	$C_{20}H_{21}ClFN_3O_2$	390.0	11.8	61
Example 62	33	$C_{20}H_{20}Cl_3N_3O_2$	440.0	15.8	72
Example 63	34	$C_{21}H_{24}ClN_3O_3$	402.5	33.8	quant
Example 64	35	$C_{22}H_{26}ClN_3O_4$	432.5	56.1	quant
Example 65	36	$C_{22}H_{26}ClN_3O_4$	432.5	37.6	quant
Example 66	37	$C_{21}H_{21}ClF_3N_3O_2$	440.0	12.6	57
Example 67	38	$C_{21}H_{24}ClN_3O_2$	386.0	12.3	64
Example 68	39	$C_{20}H_{21}Cl_2N_3O_2$	406.0	15.9	78
Example 69	40	$C_{21}H_{24}ClN_3O_2$	402.0	11.6	58
Example 70	41	$C_{20}H_{20}Cl_3N_3O_2$	442.0	17.8	81
Example 71	42	$C_{21}H_{21}ClN_4O_2$	397.5	22.4	quant
Example 72	43	$C_{21}H_{22}ClN_3O_4$	416.0	30.1	quant
Example 73	44	$C_{21}H_{20}ClF_4N_3O_2$	458.0	13.4	59
Example 74	45	$C_{21}H_{20}ClF_4N_3O_2$	458.0	13.2	58

Example 75	46	$C_{21}H_{20}ClF_4N_3O_2$	458.0	14.4	63
Example 76	47	$C_{21}H_{21}ClF_3N_3O_3$	456.0	16.4	72
Example 77	48	$C_{21}H_{20}ClF_4N_3O_2$	458	16.5	72
Example 78	49	$C_{20}H_{21}ClN_4O_4$	417.0	12.5	60
Example 79	50	$C_{21}H_{20}ClF_4N_3O_2$	458.0	26.3	quant
Example 80	51	$C_{20}H_{21}BrClN_3O_2$	450.0	8.6	38
Example 81	52	$C_{20}H_{21}ClFN_3O_2$	390.5	4.1	21
Example 82	53	$C_{20}H_{21}Cl_2N_3O_2$	406.0	5.4	27
Example 83	54	$C_{20}H_{20}Cl_3N_3O_2$	440.0	8.8	40
Example 84	55	$C_{20}H_{20}BrCl_4N_3O_2$	440.0	7.7	35
Example 85	56	$C_{21}H_{24}ClN_3O_2$	386.0	4.8	25
Example 86	57	$C_{22}H_{26}ClN_3O_4$	429.5	4.9	23
Example 87	58	$C_{20}H_{21}Cl_2N_3O_2$	406.0	4.1	20
Example 88	59	$C_{20}H_{21}BrClN_3O_2$	452.0	3.5	16
Example 89	60	$C_{26}H_{26}ClN_3O_2$	448.5	7.3	33
Example 90	61	$C_{21}H_{21}ClF_3N_3O_2$	440.0	7.1	32
Example 91	62	$C_{21}H_{24}ClN_3O_2$	386.0	10.4	54
Example 92	63	$C_{22}H_{26}ClN_3O_2$	400.5	6.0	30
Example 93	64	$C_{21}H_{21}ClN_4O_2$	397.0	7.0	35
Example 94	65	$C_{24}H_{24}ClN_3O_2$	422.0	7.7	36
Example 95	66	$C_{24}H_{24}ClN_3O_2$	422.0	6.3	30
Example 96	67	$C_{20}H_{20}ClF_2N_3O_2$	408.0	4.7	23
Example 97	68	$C_{20}H_{20}ClF_2N_3O_2$	408.0	7.8	38
Example 98	69	$C_{20}H_{20}ClF_2N_3O_2$	408.0	7.3	36
Example 99	70	$C_{20}H_{20}ClF_2N_3O_2$	408.0	9.1	45
Example 100	71	$C_{22}H_{26}ClN_3O_4$	429.0	5.6	26
Example 101	72	$C_{21}H_{21}ClF_3N_3O_2$	456.0	6.2	27
Example 102	73	$C_{21}H_{21}ClF_3N_3O_2$	456.5	16.8	74
Example 103	74	$C_{22}H_{24}ClN_3O_4$	430.0	16.4	76
Example 104	75	$C_{21}H_{20}ClF_4N_3O_2$	458.0	16.1	70
Example 105	76	$C_{21}H_{20}ClF_4N_3O_2$	458.0	17.0	74
Example 106	77	$C_{20}H_{19}ClF_3N_3O_2$	426.0	16.2	76
Example 107	78	$C_{20}H_{19}ClF_3N_3O_2$	426.0	18.0	85
Example 108	79	$C_{22}H_{20}ClF_6N_3O_2$	508.0	18.8	74
Example 109	80	$C_{22}H_{20}ClF_6N_3O_2$	508.0	16.4	65
Example 110	81	$C_{22}H_{26}ClN_3O_2$	400.0	13.9	70
Example 111	83	$C_{20}H_{21}ClN_4O_4$	417.0	16.0	77
Example 112	84	$C_{20}H_{21}ClN_4O_4$	417.0	21.6	quant
Example 113	87	$C_{23}H_{22}ClF_6N_3O_2$	522.0	17.5	67
Example 114	88	$C_{22}H_{23}ClF_3N_3O_2$	454.0	13.9	61

Example 115	89	$C_{21}H_{23}BrClN_3O_2$	466.0	15.4	66
Example 116	90	$C_{21}H_{23}ClFN_3O_2$	404.0	10.7	53
Example 117	91	$C_{21}H_{22}Cl_3N_3O_2$	456.0	13.7	60
Example 118	92	$C_{22}H_{26}ClN_3O_3$	416.0	38.4	quant
Example 119	93	$C_{23}H_{28}ClN_3O_4$	446.0	25.2	quant
Example 120	94	$C_{23}H_{28}ClN_3O_4$	446.0	16.5	74
Example 121	95	$C_{22}H_{23}ClF_3N_3O_2$	454.0	16.3	72
Example 122	96	$C_{22}H_{26}ClN_3O_2$	400.5	16.7	84
Example 123	97	$C_{21}H_{23}Cl_2N_3O_2$	420.0	11.2	53
Example 124	98	$C_{22}H_{26}ClN_3O_2$	416.5	11.8	57
Example 125	99	$C_{21}H_{22}Cl_3N_3O_2$	454.0	14.8	65
Example 126	100	$C_{22}H_{23}ClN_4O_2$	411.0	9.5	46
Example 127	101	$C_{22}H_{24}ClN_3O_4$	430.5	13.2	61
Example 128	102	$C_{22}H_{22}ClF_4N_3O_2$	472.0	13.1	56
Example 129	103	$C_{22}H_{22}ClF_4N_3O_2$	472.0	36.5	quant
Example 130	104	$C_{22}H_{22}ClF_4N_3O_2$	472.0	22.8	97
Example 131	105	$C_{22}H_{22}ClF_4N_3O_2$	472.0	20.1	85
Example 132	106	$C_{22}H_{23}ClF_3N_3O_3$	470.0	27.4	quant
Example 133	107	$C_{22}H_{22}ClF_4N_3O_2$	472.0	18.5	78
Example 134	108	$C_{21}H_{23}ClN_4O_4$	431.0	11.9	55
Example 135	109	$C_{21}H_{23}ClN_4O_4$	431.0	23.9	quant
Example 136	110	$C_{21}H_{23}ClN_4O_4$	431.0	24.4	quant
Example 137	111	$C_{23}H_{22}ClF_6N_3O_2$	522.0	9.5	36
Example 138	112	$C_{22}H_{23}ClF_3N_3O_2$	454.0	3.9	17
Example 139	113	$C_{21}H_{23}BrClN_3O_2$	466.0	7.5	32
Example 140	114	$C_{21}H_{23}ClFN_3O_2$	404.0	6.1	30
Example 141	115	$C_{21}H_{22}Cl_3N_3O_2$	456.0	6.6	29
Example 142	116	$C_{22}H_{26}ClN_3O_3$	416.0	4.8	23
Example 143	117	$C_{23}H_{28}ClN_3O_4$	446.0	6.4	29
Example 144	118	$C_{23}H_{28}ClN_3O_4$	446.0	24.6	quant
Example 145	119	$C_{22}H_{23}ClF_3N_3O_2$	454.0	5.2	23
Example 146	120	$C_{22}H_{26}ClN_3O_2$	400.5	4.4	22
Example 147	121	$C_{21}H_{23}Cl_2N_3O_2$	420.0	7.8	37
Example 148	122	$C_{22}H_{26}ClN_3O_2$	416.5	14.1	68
Example 149	123	$C_{21}H_{22}Cl_3N_3O_2$	454.0	5.4	24
Example 150	124	$C_{22}H_{23}ClN_4O_2$	411.0	34.0	quant
Example 151	125	$C_{22}H_{24}ClN_3O_4$	430.5	32.0	quant
Example 152	126	$C_{22}H_{22}ClF_4N_3O_2$	472.0	4.6	19
Example 153	127	$C_{22}H_{22}ClF_4N_3O_2$	472.0	10.4	44
Example 154	128	$C_{22}H_{22}ClF_4N_3O_2$	472.0	7.3	31

Example 155	129	$C_{22}H_{22}ClF_4N_3O_2$	472.0	13.5	57
Example 156	130	$C_{22}H_{23}ClF_3N_3O_3$	470.0	15.1	64
Example 157	131	$C_{22}H_{22}ClF_4N_3O_2$	472.0	8.6	36
Example 158	132	$C_{21}H_{23}ClN_4O_4$	431.0	4.4	20
Example 159	133	$C_{21}H_{23}ClN_4O_4$	431.0	32.0	quant
Example 160	134	$C_{21}H_{23}ClN_4O_4$	431.0	6.9	32
Example 161	135	$C_{21}H_{23}BrClN_3O_2$	466.0	7.8	34
Example 162	136	$C_{21}H_{23}ClFN_3O_2$	404.0	13.7	68
Example 163	137	$C_{21}H_{23}Cl_2N_3O_2$	420.5	14.6	69
Example 164	138	$C_{21}H_{22}Cl_3N_3O_2$	454.0	17.7	78
Example 165	139	$C_{21}H_{22}BrCl_4N_3O_2$	454.0	17.2	76
Example 166	140	$C_{22}H_{26}ClN_3O_2$	400.0	15.0	75
Example 167	141	$C_{23}H_{28}ClN_3O_4$	443.5	13.9	62
Example 168	142	$C_{21}H_{23}Cl_2N_3O_2$	420.0	13.7	65
Example 169	143	$C_{21}H_{23}BrClN_3O_2$	464.0	16.1	69
Example 170	144	$C_{27}H_{28}ClN_3O_2$	462.0	17.6	76
Example 171	145	$C_{22}H_{23}ClF_3N_3O_2$	454.0	16.0	71
Example 172	146	$C_{22}H_{26}ClN_3O_2$	400.0	14.9	75
Example 173	147	$C_{23}H_{28}ClN_3O_2$	414.0	16.2	78
Example 174	148	$C_{22}H_{23}ClN_4O_2$	411.0	14.9	73
Example 175	149	$C_{25}H_{26}ClN_3O_2$	436.0	17.1	78
Example 176	150	$C_{25}H_{26}ClN_3O_2$	436.0	13.1	60
Example 177	151	$C_{21}H_{22}ClF_2N_3O_2$	422.0	14.8	70
Example 178	152	$C_{21}H_{22}ClF_2N_3O_2$	422.0	15.3	73
Example 179	153	$C_{21}H_{22}ClF_2N_3O_2$	422.0	15.3	73
Example 180	154	$C_{21}H_{22}ClF_2N_3O_2$	422.0	16.4	78
Example 181	155	$C_{23}H_{28}ClN_3O_4$	443.0	16.9	76
Example 182	156	$C_{22}H_{23}ClF_3N_3O_2$	470.5	12.6	54
Example 183	157	$C_{22}H_{23}ClF_3N_3O_2$	470.0	20.0	85
Example 184	158	$C_{23}H_{26}ClN_3O_4$	444.0	17.4	78
Example 185	159	$C_{22}H_{22}ClF_4N_3O_2$	472.0	18.4	78
Example 186	160	$C_{22}H_{22}ClF_4N_3O_2$	472.0	19.6	83
Example 187	161	$C_{21}H_{21}ClF_3N_3O_2$	440.0	17.0	77
Example 188	162	$C_{21}H_{21}ClF_3N_3O_2$	440.0	17.1	78
Example 189	163	$C_{23}H_{22}ClF_6N_3O_2$	522.0	20.8	80
Example 190	164	$C_{23}H_{22}ClF_6N_3O_2$	522.0	2.7	10
Example 191	165	$C_{23}H_{28}ClN_3O_2$	414.0	16.4	79
Example 192	166	$C_{22}H_{23}ClF_3N_3O_2$	454.0	8.6	38
Example 193	167	$C_{21}H_{23}BrClN_3O_2$	464.0	11.6	50
Example 194	168	$C_{21}H_{23}Cl_2N_3O_2$	420.0	11.5	55

Example 195	169	$C_{21}H_{22}Cl_3N_3O_2$	454.0	10.0	44
Example 196	170	$C_{22}H_{22}ClF_4N_3O_2$	472.0	10.4	44
Example 197	171	$C_{21}H_{23}Cl_2N_3O_2$	420.0	8.9	42
Example 198	172	$C_{21}H_{24}ClN_3O_2$	386.0	10.3	53
Example 199	173	$C_{21}H_{23}ClN_4O_4$	431.0	14.6	68
Example 200	174	$C_{22}H_{23}ClF_3N_3O_2$	454.0	10.4	46
Example 201	175	$C_{21}H_{23}BrClN_3O_2$	464.0	13.4	58
Example 202	176	$C_{21}H_{23}Cl_2N_3O_2$	420.0	12.7	60
Example 203	177	$C_{21}H_{22}Cl_3N_3O_2$	454.0	13.2	58
Example 204	178	$C_{22}H_{22}ClF_4N_3O_2$	472.0	12.9	55
Example 205	179	$C_{21}H_{23}Cl_2N_3O_2$	420.0	13.3	63
Example 206	180	$C_{21}H_{24}ClN_3O_2$	386.0	24.2	quant
Example 207	181	$C_{21}H_{23}ClN_4O_4$	431.0	1.0	1
Example 208	182	$C_{23}H_{25}ClF_3N_3O_2$	468.0	15.1	65
Example 209	183	$C_{22}H_{25}BrClN_3O_2$	478.0	18.0	75
Example 210	184	$C_{22}H_{25}Cl_2N_3O_2$	434.0	16.3	75
Example 211	185	$C_{22}H_{24}Cl_3N_3O_2$	468.0	18.6	79
Example 212	186	$C_{23}H_{24}ClF_4N_3O_2$	486.0	16.5	68
Example 213	187	$C_{22}H_{25}Cl_2N_3O_2$	434.0	14.4	66
Example 214	188	$C_{22}H_{26}ClN_3O_2$	400.0	14.0	70
Example 215	189	$C_{22}H_{25}ClN_4O_4$	445.0	16.8	76
Example 216	190	$C_{26}H_{25}ClF_3N_3O_2S$	536.0	17.7	66
Example 217	191	$C_{25}H_{25}BrClN_3O_2S$	546.0	20.4	75
Example 218	192	$C_{25}H_{25}Cl_2N_3O_2S$	502.0	16.9	67
Example 219	193	$C_{25}H_{24}Cl_3N_3O_2S$	536.0	18.3	68
Example 220	194	$C_{26}H_{24}ClF_4N_3O_2S$	554.0	19.4	70
Example 221	195	$C_{25}H_{25}Cl_2N_3O_2S$	502.0	19.1	76
Example 222	196	$C_{25}H_{26}ClN_3O_2S$	468.0	16.0	68
Example 223	197	$C_{25}H_{25}ClN_4O_4S$	513.0	18.4	72
Example 224	198	$C_{26}H_{25}ClF_3N_3O_2S$	536.0	13.9	52
Example 225	199	$C_{25}H_{25}BrClN_3O_2S$	546.0	12.9	47
Example 226	200	$C_{25}H_{25}Cl_2N_3O_2S$	502.0	15.6	62
Example 227	201	$C_{25}H_{24}Cl_3N_3O_2S$	536.0	17.3	64
Example 228	202	$C_{26}H_{24}ClF_4N_3O_2S$	554.0	15.4	56
Example 229	203	$C_{25}H_{25}Cl_2N_3O_2S$	502.0	13.5	54
Example 230	204	$C_{25}H_{26}ClN_3O_2S$	468.0	13.7	59
Example 231	205	$C_{25}H_{25}ClN_4O_4S$	513.0	13.9	54
Example 232	206	$C_{24}H_{27}ClF_3N_3O_4S$	546.0	10.0	37
Example 233	207	$C_{23}H_{27}BrClN_3O_4S$	558.0	17.1	61
Example 234	208	$C_{23}H_{27}Cl_2N_3O_4S$	512.0	17.0	66

Example 235	209	$C_{23}H_{26}Cl_3N_3O_4S$	546.0	7.3	27
Example 236	210	$C_{24}H_{26}ClF_4N_3O_4S$	564.0	19.2	68
Example 237	211	$C_{23}H_{27}Cl_2N_3O_4S$	512.0	7.9	31
Example 238	212	$C_{23}H_{28}ClN_3O_4S$	478.0	13.7	57
Example 239	213	$C_{23}H_{27}ClN_4O_4S$	523.0	5.5	21

Example 240: Preparation of (*R*)-3-[*N*-{3-Fluoro-5-(trifluoromethyl)benzoyl}glycyl]amino-1-(3,5-dimethylisoxazol-4-ylmethyl)pyrrolidine (Compound No. 1191).

A solution of 3-fluoro-5-(trifluoromethyl)benzoyl chloride (0.058 mmol) in dichloromethane (1 mL) was added to a mixture of (*R*)-1-(3,5-dimethylisoxazol-4-ylmethyl)-3-(glycylamino)pyrrolidine (0.050 mmol) and piperidinomethylpolystyrene (58 mg) in chloroform (0.2 mL) and dichloromethane (0.75 mL). After the reaction mixture was stirred at room temperature for 2 h, methanol (1.0 mL) was added and the mixture was stirred at room temperature for 30 min. The reaction mixture was loaded onto Varian™ SCX column, and washed with CH_3OH (16 mL). Product was eluted off using 2 N NH_3 in CH_3OH (6 mL) and concentrated to afford (*R*)-3-[*N*-{3-fluoro-5-(trifluoromethyl)benzoyl}glycyl]amino-1-(3,5-dimethylisoxazol-4-ylmethyl)pyrrolidine (Compound No. **1191**) (19.5 mg, 88%): The purity was determined by RPLC/MS (100%); ESI/MS m/e 443.2 (M^{+}+H, $C_{20}H_{22}F_4N_4O_3$).

Examples 241-265.

The compounds of this invention were synthesized pursuant to methods of Example 240 using the corresponding reactant respectively. The ESI/MS data and yields are summarized in Table 4.

Table 4

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 241	1192	C20 H22 F4 N4 O3	443.2	19.2	87
Example 242	1193	C20 H23 F3 N4 O4	441.0	17.5	79
Example 243	1194	C21 H22 F6 N4 O3	493.0	20.4	83
Example 244	1195	C19 H23 Br N4 O3	435.1	16.8	77
Example 245	1196	C19 H23 N5 O5	402.2	16.2	81
Example 246	1197	C20 H22 F4 N4 O3	443.2	17.6	80
Example 247	1198	C19 H23 Cl N4 O3	391.0	16.5	84
Example 248	1199	C20 H26 N4 O3	371.0	16.1	87

Example 249	1200	C19 H22 Cl2 N4 O3	425.0	18.0	85
Example 250	1201	C19 H22 F2 N4 O3	393.0	16.6	85
Example 251	1202	C20 H22 F4 N4 O3	443.2	16.8	76
Example 252	1203	C22 H24 F3 N3 O3	436.2	17.1	79
Example 253	1204	C23 H23 F6 N3 O2	488.2	18.1	74
Example 254	1205	C21 H24 Br N3 O2	430.0	17.5	81
Example 255	1206	C21 H24 N4 O4	397.0	16.2	82
Example 256	1207	C22 H23 F4 N3 O2	438.2	17.5	80
Example 257	1208	C21 H24 Cl N3 O2	386.0	15.8	82
Example 258	1209	C22 H27 N3 O2	366.0	15.7	86
Example 259	1210	C21 H23 Cl2 N3 O2	420.0	17.8	85
Example 260	1211	C21 H23 F2 N3 O2	388.0	16.3	84
Example 261	1212	C22 H23 F4 N3 O2	438.2	17.4	80
Example 262	1213	C24 H24 Cl F6 N3 O2	536.2	24.0	90
Example 263	1214	C23 H24 Cl F4 N3 O3	486.2	22.2	91
Example 264	1215	C22 H24 Cl3 N3 O2	467.9	20.9	89
Example 265	1216	C22 H24 Cl F2 N3 O2	436.0	19.3	89

Example 266: Preparation of (*R*)-1-(4-Chlorobenzyl)-3-[{*N*-(4-(dimethylamino)benzoyl)glycyl}amino]pyrrolidine (Compound No. 952).

A solution of (*R*)-1-(4-chlorobenzyl)-3-(glycylamino)pyrrolidine (13.8 mg, 0.052 mmol) in $CHCl_3$ (2 mL) was treated with Et_3N (0.021 mL, 0.15 mmol), 4-(dimethylamino)benzoic acid (10 mg, 0.061 mmol), EDCI (10.2 mg, 0.053 mmol) and HOBt (7.5 mg, 0.055 mmol). The reaction mixture was stirred at room temperature for 16 h. The solution was washed with 2 N aqueous NaOH solution (2 mL x 2) and brine (2 mL), and dried by filtration through a PTFE membrane using CH_2Cl_2 (3 mL). Concentration afforded the desired material (compound No. **952**) (24.9 mg, quant): The purity was determined by RPLC/MS (91%); ESI/MS m/e 415.0 (M^++H, $C_{22}H_{27}ClN_4O_2$).

Examples 267-347.

The compounds of this invention were synthesized pursuant to methods of Example 266 using the corresponding reactant respectively. Solid-phase extraction (Varian™ SCX column) or chromatography (HPLC-C_{18}), if needed, afforded the desired material. The ESI/MS data and yields are summarized in Table 5.

Table 5

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 267	951	C22 H24 Cl N3 O4	430.0	26.3	quant
Example 268	953	C23 H29 Cl N4 O2	429.0	28.8	quant
Example 269	954	C21 H25 Cl N4 O2	401.0	27.9	quant
Example 270	955	C22 H27 Cl N4 O2	415.0	26.8	quant
Example 271	956	C21 H24 Cl N3 O3	402.0	10.3	51
Example 272	957	C20 H22 Cl N3 O3	388.0	1.4	7
Example 273	958	C21 H24 Cl N3 O3	402.5	1.2	6
Example 274	959	C22 H25 Cl N4 O3	429.5	4.7	22
Example 275	960	C23 H27 Cl N4 O3	443.0	10.9	49
Example 276	961	C21 H25 Cl N4 O2	401.0	28.4	quant
Example 277	962	C22 H27 Cl N4 O2	415.0	24.9	quant
Example 278	963	C21 H24 Cl N3 O3	402.0	4.4	22
Example 279	964	C22 H24 Cl N3 O4	430.0	29.5	quant
Example 280	965	C23 H26 Cl N3 O4	444.0	27.2	quant
Example 281	966	C22 H24 Cl N3 O3	414.0	27.0	quant
Example 282	967	C23 H26 Cl N3 O3	428.0	27.0	quant
Example 283	968	C22 H23 Cl N4 O2	411.0	21.4	quant
Example 284	969	C23 H25 Cl N4 O2	425.0	27.6	quant
Example 285	970	C22 H27 Cl N4 O2	415.0	28.6	quant
Example 286	971	C23 H29 Cl N4 O2	429.0	27.9	quant
Example 287	972	C20 H23 Cl N4 O2	387.0	26.2	quant
Example 288	973	C21 H25 Cl N4 O2	401.0	26.8	quant
Example 289	974	C20 H23 Cl N4 O2	387.0	26.6	quant
Example 290	975	C21 H25 Cl N4 O2	401.0	28.2	quant
Example 291	976	C22 H23 Cl N4 O2	411.0	29.2	quant
Example 292	977	C23 H25 Cl N4 O2	425.0	29.5	quant
Example 293	978	C20 H21 Cl N6 O2	413.0	2.2	11
Example 294	979	C21 H23 Cl N6 O2	427.0	10.2	48
Example 295	980	C22 H25 Cl N4 O3	429.0	28.8	quant
Example 296	981	C23 H27 Cl N4 O3	443.0	11.9	54
Example 297	982	C22 H27 Cl N4 O2	415.0	27.4	quant
Example 298	983	C23 H29 Cl N4 O2	429.5	28.1	quant
Example 299	984	C21 H24 Cl N3 O3	402.0	27.7	quant
Example 300	985	C22 H26 Cl N3 O3	416.0	28.6	quant
Example 301	1149	C21 H28 N4 O4	401	15.5*	38
Example 302	1150	C21 H28 N4 O3	385	10.9*	28
Example 303	1151	C21 H25 F3 N4 O3	439	17.3*	39
Example 304	1152	C21 H24 F N5 O3	415	12.7*	30

Example 305	1153	C21 H24 Cl N5 O3	430	17.5*	41
Example 306	1154	C22 H27 N5 O3	410	20.6*	50
Example 307	1155	C19 H23 F3 N4 O4	429	13.8*	32
Example 308	1156	C21 H30 N4 O4	403	17.7*	43
Example 309	1157	C18 H24 N4 O3 S2	409	12.6*	30
Example 310	1158	C19 H23 Cl2 N5 O3	440	16.9*	38
Example 311	1159	C22 H31 N5 O6	462	38.6*	85
Example 312	1160	C20 H26 Br N5 O3	464	20.4	45
Example 313	1289	C20 H27 N5 O4	403	5.8*	14
Example 314	1290	C21 H29 N5 O3	400	6.9*	17
Example 315	1291	C24 H28 N4 O2	405	22.4	68
Example 316	1292	C22 H27 Br N4 O2	461	23.8	15
Example 317	1293	C22 H23 F4 N3 O2	438	20.9	59
Example 318	1294	C22 H23 F4 N3 O2	438	20.8	59
Example 319	1295	C23 H31 N3 O3	398	17.5	54
Example 320	1296	C20 H25 N3 O2 S2	404	18.8	58
Example 321	1297	C21 H24 F3 N3 O3	424	18.1	53
Example 322	1388	C21 H32 N6 O3	417	7.4*	24
Example 323	1389	C19 H22 N6 O4	399	15.2	48
Example 324	1401	C23 H25 Cl N4 O2	425	8.3*	16
Example 325	1402	C24 H32 N4 O5	457	8.3*	15
Example 326	1403	C20 H24 N4 O2	353	14.8	52
Example 327	1404	C20 H24 N4 O2	353	17.0	60
Example 328	1405	C21 H26 N4 O2 S	399	17.3	54
Example 329	1407	C22 H28 N4 O2 S	413	19.1	57
Example 330	1410	C19 H24 N4 O3	357	9.7*	59
Example 331	1769	C22 H26 Cl F3 N4 O5	519	11.6*	20
Example 332	1770	C26 H28 Cl2 N6 O4	559	13.1*	21
Example 333	1771	C26 H37 N5 O4	484	12.7*	23
Example 334	1772	C28 H39 N5 O4	510	5.5*	9
Example 335	1773	C28 H37 N5 O4	509	6.2*	11
Example 336	1774	C28 H34 N6 O6	551	13.6*	22
Example 337	2039	C19 H24 N4 O2	341	5.2*	14
Example 338	2040	C22 H27 N3 O4	398	2.0*	5
Example 339	2041	C23 H29 N3 O3	396	6.2*	15
Example 340	2042	C25 H37 N3 O2	413	2.6*	6
Example 341	2043	C24 H31 N3 O2	394	6.8*	17
Example 342	2044	C25 H28 N4 O4	449	8.7*	16
Example 343	2045	C26 H29 Cl N6 O4	525	11.4*	19
Example 344	2046	C27 H32 N6 O4	505	7.7*	13

Example 345	2047	C28 H32 N4 O4	489	10.0*	18
Example 346	2048	C28 H37 N5 O5	524	3.7*	6
Example 347	2049	C28 H37 N5 O4	509	5.3*	9

*Yield of TFA salt.

Example 348: Preparation of (*R*)-1-(4-Chlorobenzyl)-3-[{*N*-(2-amino-5-chlorobenzoyl)glycyl}amino]pyrrolidine (Compound No. 1084).

A solution of (*R*)-1-(4-chlorobenzyl)-3-(glycylamino)pyrrolidine (0.050 mmol) in $CHCl_3$ (2 mL) was treated with 2-amino-5-chlorobenzoic acid (0.060 mmol) and diisopropylcarbodiimide (0.060 mmol). The reaction mixture was stirred at room temperature for 15 h. The mixture was loaded onto Varian™ SCX column, and washed with CH_3OH (15 mL). Product was eluted off using 2 N NH_3 in CH_3OH (5 mL) and concentrated to afford (*R*)-1-(4-chlorobenzyl)-3-{*N*-(2-amino-5-chlorobenzoyl)glycyl}amino]pyrrolidine (Compound No. **1084**) (12.7 mg, 60%): The purity was determined by RPLC/MS (87%); ESI/MS m/e 421.0 (M^++H, $C_{20}H_{22}Cl_2N_4O_2$).

Examples 349-361.

The compounds of this invention were synthesized pursuant to methods of Example 348 using the corresponding reactant respectively. If the starting amine remained, treatment with isocyanatomethylated polystyrene (50 mg) in $CHCl_3$ (1 mL) at room temperature, filtration and concentration afforded the desired material. The ESI/MS data and yields are summarized in Table 6.

Table 6

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 349	1085	$C_{20}H_{22}ClN_5O_4$	432.0	4.1	19
Example 350	1086	$C_{20}H_{23}ClN_4O_2$	387.0	7.9	41
Example 351	1087	$C_{22}H_{23}ClN_4O_2$	411.0	15.0	73
Example 352	1088	$C_{18}H_{20}ClN_3O_3$	362.0	12.9	71
Example 353	1089	$C_{22}H_{22}ClFN_4O_2$	429.0	16.0	75
Example 354	1090	$C_{22}H_{26}ClN_3O_3$	416.0	15.8	76
Example 355	1091	$C_{21}H_{24}Cl_2N_4O_2$	435.0	10.9	50
Example 356	1092	$C_{21}H_{24}ClN_5O_4$	446.0	7.9	35
Example 357	1093	$C_{21}H_{25}ClN_4O_2$	401.0	9.5	47
Example 358	1094	$C_{23}H_{25}ClN_4O_2$	425.0	15.8	74
Example 359	1095	$C_{19}H_{22}ClN_3O_3$	376.0	13.5	72
Example 360	1096	$C_{23}H_{24}ClFN_4O_2$	443.0	11.8	53

Example 361	1097	$C_{23}H_{28}ClN_3O_3$	430.0	15.1	70

Example 362: Preparation of (*R*)-1-(4-Chlorobenzyl)-3-[{*N*-(3-bromo-4-methylbenzoyl)glycyl}amino]pyrrolidine (Compound No. 1098).

A solution of (*R*)-1-(4-chlorobenzyl)-3-(glycylamino)pyrrolidine (0.050 mmol) in $CHCl_3$ (1.35 mL) and *tert*-butanol (0.15 mL) was treated with 3-bromo-4-methylbenzoic acid (0.060 mmol), diisopropylcarbodiimide (0.060 mmol), and HOBt (0.060 mmol). The reaction mixture was stirred at room temperature for 15 h. The mixture was loaded onto Varian™ SCX column, and washed with $CH_3OH/CHCl_3$ 1:1 (12 mL) and CH_3OH (12 mL). Product was eluted off using 2 N NH_3 in CH_3OH (5 mL) and concentrated to afford (*R*)-1-(4-chlorobenzyl)-3-[{*N*-(3-bromo-4-methylbenzoyl)glycyl}amino]pyrrolidine (Compound No. **1098**) (11.6 mg, 50%): The purity was determined by RPLC/MS (94%); ESI/MS m/e 466.0 ($C_{21}H_{23}BrClN_3O_2$).

Examples 363-572.

The compounds of this invention were synthesized pursuant to methods of Example 362 using the corresponding reactant respectively. Preparative TLC, if needed, afforded the desired material. The ESI/MS data and yields are summarized in Table 7.

The following 3 compounds were obtained as byproduct of Compound Nos. **1415**, **1416**, and **1417**, respectively.

1419: 7.9 mg, 38% yield; ESI/MS m/e 419.0 ($C_{20}H_{23}ClN_4O_2S$).

1420: 7.1 mg, 36% yield; ESI/MS m/e 399.2 ($C_{21}H_{26}N_4O_2S$).

1421: 7.4 mg, 37% yield; ESI/MS m/e 404.2 ($C_{19}H_{25}$N5O3S).

Table 7

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 363	1099	$C_{20}H_{20}BrClFN_3O_2$	470.0	3.1	13
Example 364	1100	$C_{20}H_{20}Cl_2FN_3O_2$	424.0	3.1	15
Example 365	1101	$C_{21}H_{23}ClIN_3O_2$	512.0	12.5	49
Example 366	1102	$C_{21}H_{23}ClN_4O_4$	431.2	7.7	36
Example 367	1103	$C_{22}H_{26}BrN_3O_2$	446.0	13.8	62
Example 368	1104	$C_{21}H_{23}BrFN_3O_2$	450.0	16.5	74
Example 369	1105	$C_{21}H_{23}ClFN_3O_2$	404.2	14.7	73
Example 370	1106	$C_{22}H_{26}IN_3O_2$	492.0	18.5	75

Example 371	1107	$C_{22}H_{26}N_4O_4$	411.2	15.2	74
Example 372	1108	$C_{20}H_{25}BrN_4O_3$	449.0	12.8	57
Example 373	1109	$C_{19}H_{22}BrFN_4O_3$	455.0	16.2	71
Example 374	1110	$C_{19}H_{22}ClFN_4O_3$	409.2	14.4	70
Example 375	1111	$C_{20}H_{25}IN_4O_3$	497.0	17.9	72
Example 376	1112	$C_{20}H_{25}N5O_5$	416.2	14.9	72
Example 377	1113	$C_{23}H_{27}BrClN_3O_2$	494.0	16.1	65
Example 378	1114	$C_{22}H_{24}BrClFN_3O_2$	498.0	20.2	81
Example 379	1115	$C_{22}H_{24}Cl_2FN_3O_2$	452.2	18.6	82
Example 380	1116	$C_{23}H_{27}ClIN_3O_2$	539.1	21.9	81
Example 381	1117	$C_{23}H_{27}ClN_4O_4$	459.2	18.7	81
Example 382	1171	$C_{21}H_{23}BrClN_3O_2$	466.0	4.9	21
Example 383	1172	$C_{22}H_{23}ClN_4O_3$	427.2	16.1	75
Example 384	1173	$C_{23}H_{25}ClN_4O_3$	441.2	22.8	quant
Example 385	1174	$C_{20}H_{22}ClFN_4O_2$	405.2	21.4	quant
Example 386	1175	$C_{22}H_{26}BrN_3O_2$	446.0	15.8	71
Example 387	1176	$C_{23}H_{26}N_4O_3$	407.2	17.6	87
Example 388	1177	$C_{24}H_{28}N_4O_3$	421.2	20.2	96
Example 389	1178	$C_{21}H_{25}FN_4O_2$	385.0	16.2	84
Example 390	1179	$C_{21}H_{25}N_5O_4$	412.2	2.3	11
Example 391	1180	$C_{23}H_{26}N_4O_2$	391.0	21.6	quant
Example 392	1181	$C_{20}H_{25}BrN_4O_3$	451.0	20.1	89
Example 393	1182	$C_{21}H_{25}N_5O_4$	412.2	13.3	65
Example 394	1183	$C_{22}H_{27}N_5O_4$	426.2	20.9	98
Example 395	1184	$C_{19}H_{24}FN_5O_3$	390.0	20.0	quant
Example 396	1185	$C_{19}H_{24}N_6O_5$	417.2	18.2	87
Example 397	1186	$C_{21}H_{25}N_5O_3$	396.2	17.6	89
Example 398	1187	$C_{23}H_{27}BrClN_3O_2$	494.0	22.1	90
Example 399	1188	$C_{24}H_{27}ClN_4O_3$	455.2	17.2	76
Example 400	1189	$C_{25}H_{29}ClN_4O_3$	469.2	21.1	90
Example 401	1190	$C_{22}H_{26}ClFN_4O_2$	433.2	20.4	94
Example 402	1217	$C_{21}H_{20}Cl_2F_3N_3O_2$	474.0	38.5	81
Example 403	1218	$C_{21}H_{23}ClFN_3O_2$	404.2	35.6	88
Example 404	1219	$C_{21}H_{23}Cl_2N_3O_2$	420.0	3.7	9
Example 405	1220	$C_{20}H_{22}ClIN_4O_2$	513.0	53.0	quant
Example 406	1221	$C_{20}H_{21}ClF_2N_4O_2$	423.0	38.7	92
Example 407	1222	$C_{19}H_{23}ClN_4O_2$	375.2	33.6	90
Example 408	1223	$C_{26}H_{26}ClN_3O_2S$	496.0	43.7	88
Example 409	1224	$C_{20}H_{21}ClN_4O_5$	433.0	40.6	94
Example 410	1225	$C_{22}H_{23}ClF_3N_3O_2$	454.2	18.4	41

Example 411	1226	$C_{22}H_{26}FN_3O_2$	384.0	17.1	45
Example 412	1227	$C_{22}H_{26}ClN_3O_2$	400.2	17.5	44
Example 413	1228	$C_{21}H_{25}IN_4O_2$	493.0	23.3	47
Example 414	1229	$C_{21}H_{24}F_2N_4O_2$	403.2	18.4	46
Example 415	1230	$C_{20}H_{26}N_4O_2$	355.2	15.7	44
Example 416	1231	$C_{27}H_{29}N_3O_2S$	476.0	20.9	88
Example 417	1232	$C_{21}H_{24}N_4O_5$	413.0	19.9	96
Example 418	1233	$C_{20}H_{22}ClF_3N_4O_3$	459.0	19.4	85
Example 419	1234	$C_{20}H_{25}FN_4O_3$	389.0	17.8	92
Example 420	1235	$C_{20}H_{25}ClN_4O_3$	405.2	18.7	92
Example 421	1236	$C_{19}H_{24}IN_5O_3$	498.0	23.9	96
Example 422	1237	$C_{19}H_{23}F_2N_5O_3$	408.2	19.0	93
Example 423	1238	$C_{18}H_{25}N_5O_3$	360.0	16.3	91
Example 424	1239	$C_{25}H_{28}N_4O_3S$	481.2	21.4	89
Example 425	1240	$C_{19}H_{23}N_5O_6$	418.0	19.9	95
Example 426	1241	$C_{23}H_{24}Cl_2F_3N_3O_2$	502.0	22.5	90
Example 427	1242	$C_{23}H_{27}ClFN_3O_2$	432.2	21.2	98
Example 428	1243	$C_{23}H_{27}Cl_2N_3O_2$	448.0	21.6	96
Example 429	1244	$C_{22}H_{26}ClIN_4O_2$	541.0	26.4	98
Example 430	1245	$C_{22}H_{25}ClF_2N_4O_2$	451.0	21.3	94
Example 431	1246	$C_{21}H_{27}ClN_4O_2$	403.2	19.4	96
Example 432	1247	$C_{28}H_{30}ClN_3O_2S$	524.0	24.7	94
Example 433	1248	$C_{22}H_{25}ClN_4O_5$	461.0	20.7	90
Example 434	1249	C20 H20 Cl2 N4 O4	451.0	7.4	33
Example 435	1250	C21 H23 Cl N4 O4	431.2	15.5	72
Example 436	1251	C19 H22 Cl N5 O5	436.0	22.9	quant
Example 437	1252	C23 H28 Cl N3 O2	414.2	17.9	86
Example 438	1253	C24 H31 N3 O2	394.2	15.8	80
Example 439	1254	C22 H30 N4 O3	399.2	17.3	87
Example 440	1255	C20 H22 Br Cl N4 O2	467.0	21.3	91
Example 441	1256	C21 H25 Br N4 O2	445.0	20.7	93
Example 442	1257	C19 H24 Br N5 O3	450.0	21.8	97
Example 443	1258	C21 H25 Cl N4 O2	401.2	18.1	90
Example 444	1259	C19 H24 Cl N5 O3	406.0	20.1	99
Example 445	1260	C23 H29 N3 O3	396.2	16.8	85
Example 446	1261	C23 H30 Cl N3 O3	432.2	19.8	92
Example 447	1262	C24 H33 N3 O3	412.2	17.4	85
Example 448	1263	C22 H32 N4 O4	417.2	18.7	90
Example 449	1264	C25 H26 Cl N3 O3	452.2	29.1	quant
Example 450	1265	C26 H29 N3 O3	432.2	18.1	84

Example 451	1266	C24 H28 N4 O4	437.2	19.3	88
Example 452	1267	$C_{23}H_{22}ClF_3N_4O_3$	495.2	20.6	83
Example 453	1268	$C_{21}H_{23}Cl_2N_3O_3$	436.0	17.5	80
Example 454	1269	$C_{20}H_{21}BrClN_3O_3$	468.0	19.2	82
Example 455	1270	$C_{20}H_{21}Cl_2N_3O_3$	422.2	17.3	82
Example 456	1271	$C_{20}H_{20}ClFN_4O_4$	435.0	17.1	79
Example 457	1272	$C_{24}H_{25}F_3N_4O_3$	475.2	21.7	91
Example 458	1273	$C_{22}H_{26}ClN_3O_3$	416.2	17.8	86
Example 459	1274	$C_{21}H_{24}BrN_3O_3$	448.0	19.5	87
Example 460	1275	$C_{21}H_{24}ClN_3O_3$	402.2	16.7	83
Example 461	1276	$C_{21}H_{23}FN_4O_4$	415.2	18.1	87
Example 462	1277	$C_{22}H_{24}F_3N_5O_4$	480.2	20.3	85
Example 463	1278	$C_{20}H_{25}ClN_4O_4$	421.2	18.6	88
Example 464	1279	$C_{19}H_{23}BrN_4O_4$	451.0	21.3	94
Example 465	1280	$C_{19}H_{23}ClN_4O_4$	407.2	19.1	94
Example 466	1281	$C_{19}H_{22}FN_5O_5$	420.2	19.1	91
Example 467	1282	$C_{25}H_{26}ClF_3N_4O_3$	523.2	25.0	96
Example 468	1283	$C_{23}H_{27}Cl_2N_3O_3$	464.2	12.2	53
Example 469	1284	$C_{22}H_{25}BrClN_3O_3$	496.0	24.1	97
Example 470	1285	$C_{22}H_{25}Cl_2N_3O_3$	450.2	21.8	97
Example 471	1321	$C_{20}H_{20}BrCl_2N_3O_2$	486.0	5.1	21
Example 472	1322	$C_{21}H_{23}Cl_2N_3O_2$	420.0	10.5	50
Example 473	1323	$C_{20}H_{20}Cl_2IN_3O_2$	532.0	7.1	27
Example 474	1324	$C_{21}H_{24}ClN_3O_3$	402.2	22.2	quant
Example 475	1325	$C_{27}H_{26}ClN_3O_3$	476.0	22.2	93
Example 476	1326	$C_{20}H_{21}ClIN_3O_3$	514.0	26.9	quant
Example 477	1327	$C_{21}H_{25}ClN_4O_2$	401.2	24.2	quant
Example 478	1328	$C_{21}H_{23}BrClN_3O_2$	466.0	23.1	99
Example 479	1329	$C_{22}H_{26}ClN_3O_2$	400.2	16.4	82
Example 480	1330	$C_{21}H_{23}ClIN_3O_2$	512.2	20.8	81
Example 481	1331	$C_{21}H_{24}N_3O_3$	382.2	19.6	quant
Example 482	1332	$C_{28}H_{29}N_3O_3$	456.2	21.1	93
Example 483	1333	$C_{21}H_{24}IN_3O_3$	494.0	25.3	quant
Example 484	1334	$C_{22}H_{28}N_4O_2$	381.2	19.0	quant
Example 485	1335	$C_{19}H_{22}BrClN_4O_3$	471.0	25.8	quant
Example 486	1336	$C_{20}H_{25}ClN_4O_3$	405.2	18.5	91
Example 487	1337	$C_{19}H_{22}ClIN_4O_3$	517.0	23.1	89
Example 488	1338	$C_{20}H_{26}N_4O4$	387.2	20.6	quant
Example 489	1339	$C_{26}H_{28}N_4O_4$	461.2	23.7	quant
Example 490	1340	$C_{19}H_{23}IN_4O_4$	499.0	28.2	quant

Example 491	1341	$C_{20}H_{26}N_4O_4$	386.0	20.5	quant
Example 492	1342	$C_{22}H_{24}BrCl_2N_3O_2$	514.0	27.2	quant
Example 493	1343	$C_{23}H_{27}Cl_2N_3O_2$	448.0	21.4	95
Example 494	1344	$C_{22}H_{24}Cl_2IN_3O_2$	560.0	27.0	96
Example 495	1345	$C_{23}H_{28}ClN_3O_3$	430.2	23.8	quant
Example 496	1346	$C_{22}H_{25}ClIN_3O_3$	542.0	29.4	quant
Example 497	1347	$C_{19}H_{22}ClN_3O_2S$	392.0	16.9	43
Example 498	1348	$C_{20}H_{25}N_3O_2S$	372.2	6.9	19
Example 499	1349	$C_{18}H_{24}N_4O_3S$	377.2	8.1	43
Example 500	1350	$C_{21}H_{26}ClN_3O_2S$	420.0	13.0	62
Example 501	1351	$C_{22}H_{24}BrClN_4O_3$	509.2	5.0	10
Example 502	1352	$C_{23}H_{27}BrN_4O_3$	489.2	3.6	15
Example 503	1353	$C_{21}H_{26}BrN_5O_4$	494.0	2.8	11
Example 504	1354	$C_{24}H_{28}BrClN_4O_3$	537.2	5.2	19
Example 505	1355	C21 H22 Cl N5 O2	412.0	25.5	quant
Example 506	1356	C22 H25 N5 O2	392.0	16.5	84
Example 507	1357	C20 H24 N6 O3	397.2	19.9	quant
Example 508	1358	C23 H26 Cl N5 O2	440.2	21.8	99
Example 509	1368	$C_{21}H_{20}Cl_2F_3N_3O_2$	474.0	18.4	78
Example 510	1369	$C_{24}H_{24}ClF_6IN_3O_4$	568.0	24.1	85
Example 511	1370	$C_{18}H_{19}BrClN_3O_2S$	458.0	19.4	85
Example 512	1371	$C_{26}H_{26}ClN_3O_4S$	512.2	22.1	86
Example 513	1372	$C_{26}H_{26}ClN_3O_2$	448.0	19.1	85
Example 514	1373	$C_{22}H_{23}ClF_3N_3O_2$	454.2	16.2	71
Example 515	1374	$C_{25}H_{27}F_6IN_3O_4$	548.2	22.1	81
Example 516	1375	$C_{19}H_{22}BrN_3O_2S$	436.0	17.1	78
Example 517	1376	$C_{27}H_{29}N_3O_4S$	492.0	19.4	79
Example 518	1377	$C_{27}H_{29}N_3O_2$	428.2	18.1	85
Example 519	1378	$C_{20}H_{22}ClF_3N_4O_3$	459.0	17.3	75
Example 520	1379	$C_{23}H_{26}F_6IN_4O_5$	553.2	21.0	76
Example 521	1380	$C_{17}H_{21}BrN_4O_3S$	443.0	16.4	74
Example 522	1381	$C_{25}H_{28}N_4O_5S$	497.0	18.4	74
Example 523	1382	$C_{25}H_{28}N_4O_3$	433.2	17.3	80
Example 524	1383	$C_{23}H_{24}Cl_2F_3N_3O_2$	502.0	20.0	80
Example 525	1384	$C_{20}H_{23}BrClN_3O_2S$	486.0	21.0	87
Example 526	1385	$C_{28}H_{30}ClN_3O_4S$	540.2	23.8	88
Example 527	1386	$C_{28}H_{30}ClN_3O_2$	476.0	20.0	84
Example 528	1411	$C_{22}H_{24}Cl_2N_4O_3$	463.0	0.4	2
Example 529	1412	$C_{23}H_{27}ClN_4O_2$	443.0	1.3	6
Example 530	1413	$C_{21}H_{26}ClN_5O_4$	448.0	1.1	5

Example 531	1414	$C_{24}H_{28}Cl_2N_4O_3$	491.0	0.8	3
Example 532	1415	$C_{21}H_{22}ClN_5O_2S$	444.0	6.8	31
Example 533	1416	$C_{22}H_{25}N_5O_2S$	424.0	4.8	23
Example 534	1417	$C_{20}H_{24}N_6O_3S$	429.2	4.5	21
Example 535	1418	$C_{23}H_{26}ClN_5O_2S$	472.0	10.4	44
Example 536	1423	C27 H26 Cl N3 O3	476.0	23.9	quant
Example 537	1424	C27 H29 N3 O4 S	456.2	28.0	quant
Example 538	1425	C26 H28 N4 O4	461.2	22.3	97
Example 539	1426	C29 H30 Cl N3 O3	504.2	26.8	quant
Example 540	1583	C21 H22 Cl F3 N4 O2	455.0	14.6	64
Example 541	1584	C21 H22 Cl F3 N4 O3	471.0	17.4	74
Example 542	1585	C19 H20 Br Cl N4 O2	453.0	15.6	69
Example 543	1586	C19 H20 Cl2 N4 O2	407.2	2.3	11
Example 544	1587	C26 H26 Cl N3 O3	464.0	15.4	66
Example 545	1588	C20 H23 Cl N4 O2	387.0	14.8	77
Example 546	1589	C22 H25 F3 N4 O2	435.2	11.1	51
Example 547	1590	C20 H25 F3 N4 O3	451.2	16.3	72
Example 548	1591	C20 H23 Br N4 O2	433.0	15.4	71
Example 549	1592	C20 H23 Cl N4 O2	387.0	15.6	81
Example 550	1593	C27 H29 N3 O3	444.2	14.8	67
Example 551	1594	C20 H24 F3 N5 O3	440.2	16.2	74
Example 552	1595	C20 H24 F3 N5 O4	456.2	15.4	68
Example 553	1596	C18 H22 Br N5 O3	436.0	15.6	72
Example 554	1597	C18 H22 Cl N5 O3	391.8	14.4	73
Example 555	1598	C25 H28 N4 O4	449.2	15.9	71
Example 556	1599	C19 H25 N5 O3	372.2	15.8	85
Example 557	1606	C21 H21 Cl F3 N3 O2 S	472.0	17.0	72
Example 558	1607	C21 H21 Cl F3 N3 O2 S	452.2	15.3	68
Example 559	1608	C20 H23 F3 N4 O3 S	457.2	15.9	70
Example 560	1660	C21 H22 Br F3 N4 O2	501.0	19.0	76
Example 561	1661	C21 H22 Br F3 N4 O3	517.0	16.2	63
Example 562	1662	C20 H21 Br F2 N4 O2	469.0	15.1	65
Example 563	1663	C20 H22 Br Cl N4 O2	467.0	14.5	62
Example 564	1692	C20 H23 Br2 N3 O3	514	7.3	28
Example 565	1693	C22 H26 F2 N4 O2	417	16.2	78
Example 566	1694	C22 H27 F N4 O2	399	21.8	quant
Example 567	1695	C22 H27 Br N4 O2	459	24.5	quant
Example 568	1696	C22 H27 I N4 O2	507	27.4	quant
Example 569	1697	C22 H27 Cl N4 O2	415	22.1	quant
Example 570	1698	C23 H27 F3 N4 O3	465	24.3	quant

Example 571	1699	C23 H27 F3 N4 O2	449	25.3	quant
Example 572	1700	C22 H25 Br Cl N3 O2	480	17.8	74

For example, Compound No. **1583** showed the following NMR spectra: ^{1}H NMR (400 MHz, CD_3OD) δ 1.64-1.72 (m, 1 H), 2.20-2.30 (m, 1 H), 2.41-2.51 (m, 2 H), 2.71-2.78 (m, 2 H), 3.59 (dd, J = 15.4, 12.9 Hz, 2 H), 3.94 (s, 2 H), 4.35-4.41 (m, 1 H), 6.82 (d, J = 8.6 Hz, 1 H), 7.29 (s, 4 H), 7.40 (dd, J = 8.6, 1.7 Hz, 1 H), 7.85 (d, J = 0.96 Hz, 1 H).

Reference Example 4: Preparation of (*S*)-3-[*N*-{3-(trifluoromethyl)benzoyl}glycyl]aminopyrrolidine.

A suspension of (*S*)-1-(4-chlorobenzyl)-3-[*N*-{3-(trifluoromethyl)benzoyl}glycyl]aminopyrrolidine (2.93 g, 6.66 mmol) and $Pd(OH)_2$ in 5% HCO_2H/methanol (70 mL) was stirred at 60 °C for 3 h. The Pd catalyst was filtered off through Celite, and the filtrate was concentrated. To the residue was added 2N aqueous NaOH solution (100 mL) and the mixture was extracted with ethyl acetate (100 mL x 3). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography (SiO_2, AcOEt/MeOH/Et_3N = 85/10/5-60/30/5) gave (*S*)-3-[*N*-{3-(trifluoromethyl)benzoyl}glycyl]aminopyrrolidine (1.70 g, 81%) as an oil: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.76 (d, J = 7.3 Hz, 1 H), 2.07-2.25 (m, 1 H), 2.81-2.98 (m, 2 H), 3.02-3.11 (m, 2 H), 4.12 (s, 2 H), 4.41 (br, 1 H), 6.90 (br, 1 H), 7.45 (br, 1 H), 7.58 (dd, J = 7.3 and 7.3 Hz, 1 H), 7.77 (d, J = 7.3 Hz, 1 H), 8.02 (d, J = 7.3 Hz, 1 H), 8.11 (s, 1 H) ; ESI/MS m/e 316.0 (M^++H, $C_{14}H_{16}F_3N_3O_2$).

(*R*)-3-[*N*-{3-(Trifluoromethyl)benzoyl}glycyl]aminopyrrolidine was also prepared pursuant to the above method using the corresponding reactant: 1.49 g, 68%; The product showed the same ^{1}H NMR and ESI/MS with those of (*S*)-isomer.

(*R*)-3-[*N*-{2-Amino-5-(trifluoromethyl)benzoyl}glycyl]aminopyrrolidine was also prepared pursuant to the above method using the corresponding reactant: 316 mg, 93%; ESI/MS m/e 331.2 (M^++H, $C_{14}H_{17}F_3N_4O_2$).

(*R*)-3-[*N*-{2-(*tert*-Butoxycarbonylamino)-5-(trifluoromethoxy)benzoyl}glycyl]aminopyrrolidine was also prepared pursuant to the above method using the corresponding reactant: quant; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.51 (s, 9 H), 1.60-1.70 (m, 2 H), 2.10-2.25 (m, 1 H), 2.80-2.88 (m, 1 H), 2.89-2.98 (m, 1 H), 3.04-3.18 (m, 2 H), 4.05 (d, J = 4.9 Hz, 2 H), 4.43 (br, 1 H), 6.15 (br, 1 H), 7.03 (br, 1 H), 7.32 (d, J = 9.3 Hz, 1 H), 7.38 (s, 1 H), 8.42 (d, J = 9.3 Hz, 1 H).

Example 573: Preparation of (*R*)-3-[{*N*-(2-(*tert*-Butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-chlorobenzyl)pyrrolidine.

A solution of (*R*)-1-(4-chlorobenzyl)-3-(glycylamino)pyrrolidine (5.0 g, 18.7 mmol) in dichloromethane (100 mL) was treated with Et_3N (2.9 mL, 20.5 mmol), 2-(*tert*-butoxycarbonylamino)-5-(trifluoromethyl)benzoic acid (6.27 g, 20.5 mmol), EDCI (3.9 g, 20.5 mmol) and HOBt (2.8 g, 20.5 mmol). The reaction mixture was stirred at room temperature overnight. To the reaction mixture was added 2 N aqueous NaOH solution (80 mL) and the mixture was extracted with dichloromethane. The extract was dried over anhydrous Na_2SO_4, filtered, and evaporated. Column chromatography (SiO_2, hexane/ethyl acetate = 1/1-1/4) afforded (*R*)-3-[{*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-chlorobenzyl)pyrrolidine (9.41 g, 91%) as a white amorphous solid: ESI/MS m/e 555.2 (M^++H, $C_{26}H_{30}ClF_3N_4O_4$).

Reference Example 5: Preparation of (*R*)-3-[{*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine.

A mixture of (*R*)-3-[{*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-chlorobenzyl)pyrrolidine (6.3 g, 11.4 mmol), $Pd(OH)_2$ (1.68 g), HCO_2H (3.7 mL), and methanol (80 mL) was stirred at 50 °C overnight. After the mixture was cooled to room temperature, the Pd catalyst was filtered off through Celite and the filtrate was concentrated. Column chromatography (SiO_2, AcOEt, AcOEt/MeOH = 5/1-4/1) gave (*R*)-3-[{*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine (4.42 g, 90%) as a white solid: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.48 (s, 9 H), 2.0-2.4 (m, 2 H), 3.42-3.71 (m, 5 H), 4.00-4.22 (m, 2 H), 4.56 (br, 1 H), 7.48 (d, J = 9.0 Hz, 1 H), 7.93 (s, 1 H), 8.17 (br, 1 H), 8.33 (d, J = 9.0 Hz, 1 H), 8.45 (br, 1 H).

Example 574: Preparation of (*S*)-1-Benzyl-3-[*N*-{3-(trifluoromethyl)benzoyl}glycyl]aminopyrrolidine (Compound No. 239).

A solution of (*S*)-3-[*N*-{3-(trifluoromethyl)benzoyl}glycyl]aminopyrrolidine (0.060 mmol) in CH_3CN (1.1 mL) and (piperidinomethyl)polystyrene (2.6-2.8 mmol/g, 30 mg) were added to a solution of benzyl bromide (0.050 mmol) in CH_3CN (0.4 mL). The reaction mixture was stirred at 45 °C for 5 h. After the mixture was cooled to room temperature, the resin was removed by filtration and the filtrate was concentrated. The residue was resolved in CH_3CN (1.0 mL) and phenyl isocyanate (0.008 mL, 0.05

mmol) was added. The mixture was stirred at room temperature for 1 h, loaded onto Varian™ SCX column, and washed with CH_3OH (15 mL). Product was eluted off using 2 N NH_3 in CH_3OH (6 mL) and concentrated to afford (*S*)-1-benzyl-3-[*N*-{3-(trifluoromethyl)benzoyl}glycyl]aminopyrrolidine (compound No. **239**) (9.0 mg, 44%): The purity was determined by RPLC/MS (99%); ESI/MS m/e 406.0 (M^++H, $C_{21}H_{22}F_3N_3O_2$).

Example 575: Preparation of (*R*)-1-(4-Butylbenzyl)-3-[{*N*-(3-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine (Compound No. 1648).

To a mixture of (*R*)-3-[*N*-{3-(trifluoromethyl)benzoyl}glycyl]aminopyrrolidine (0.050 mmol), 4-butylbenzaldehyde (0.18 mmol), $NaBH_3CN$ (0.23 mmol), and methanol (1.85 mL) was added acetic acid (0.060 mL). The reaction mixture was stirred at 60 °C for 12 h. The mixture was cooled to room temperature, loaded onto Varian™ SCX column, and washed with CH_3OH (15 mL). Product was eluted off using 2 N NH_3 in CH_3OH (5 mL) and concentrated to afford (*R*)-1-(4-butylbenzyl)-3-[{*N*-(3-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine (Compound No. **1648**) (20.6 mg, 89%): The purity was determined by RPLC/MS (91%); ESI/MS m/e 462.2 (M^++H, $C_{25}H_{30}F_3N_3O_2$).

Examples 576-738.

The compounds of this invention were synthesized pursuant to methods of Examples 574or 575 using the corresponding reactant respectively. Preparative TLC or chromatography (HPLC-C_{18}), if needed, afforded the desired material. The ESI/MS data and yields are summarized in Table 8.

Table 8

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 576	240	$C_{21}H_{21}F_4N_3O_2$	424.0	10.2	48
Example 577	241	$C_{21}H_{21}ClF_3N_3O_2$	440.0	12.1	55
Example 578	242	$C_{21}H_{20}Cl_2F_3N_3O_2$	474.0	13.9	59
Example 579	243	$C_{21}H_{20}Cl_2F_3N_3O_2$	474.0	13.8	58
Example 580	244	$C_{22}H_{24}F_3N_3O_2$	420.0	13.1	62
Example 581	245	$C_{21}H_{21}F_4N_3O_2$	424.0	11.9	56
Example 582	246	$C_{21}H_{21}ClF_3N_3O_2$	440.0	8.5	39
Example 583	247	$C_{21}H_{20}Cl_2F_3N_3O_2$	474.0	10.5	44
Example 584	248	$C_{22}H_{24}CF_3N_3O_3$	436.0	11.0	51

Example 585	249	$C_{22}H_{21}ClF_6N_3O_2$	474.0	12.8	54
Example 586	250	$C_{22}H_{24}F_3N_3O_2$	420.0	11.0	52
Example 587	251	$C_{21}H_{21}F_4N_3O_2$	424.0	13.5	64
Example 588	252	$C_{22}H_{24}F_3N_3O_3$	436.0	11.8	54
Example 589	253	$C_{22}H_{24}F_3N_3O_2$	420.0	11.1	53
Example 590	254	$C_{21}H_{20}ClF_3N_4O_4$	485.0	2.4	10
Example 591	255	$C_{21}H_{21}F_3N_4O_4$	451.0	12.2	54
Example 592	256	$C_{21}H_{21}F_3N_4O_4$	451.0	11.4	51
Example 593	257	$C_{22}H_{21}F_6N_3O_2$	474.0	11.1	47
Example 594	258	$C_{24}H_{26}F_3N_3O_4$	478.0	15.3	64
Example 595	259	$C_{22}H_{23}ClF_3N_3O_2$	420.0	6.4	31
Example 596	260	$C_{21}H_{20}Cl_2F_3N_3O_2$	474.0	12.1	51
Example 597	261	$C_{22}H_{21}ClF_6N_3O_2$	474.0	13.6	57
Example 598	262	$C_{21}H_{21}BrF_3N_3O_2$	484.0	15.2	63
Example 599	263	$C_{21}H_{21}BrF_3N_3O_2$	484.0	14.5	60
Example 600	264	$C_{27}H_{26}F_3N_3O_3$	498.0	9.3	37
Example 601	265	$C_{21}H_{21}BrF_3N_3O_2$	484.0	11.6	48
Example 602	266	$C_{22}H_{22}F_3N_3O_4$	450.0	8.9	40
Example 603	267	$C_{22}H_{24}F_3N_3O_3$	436.0	10.3	47
Example 604	268	$C_{23}H_{25}F_3N_4O_3$	463.0	6.3	27
Example 605	269	$C_{22}H_{24}F_3N_3O_4S$	484.0	8.0	33
Example 606	270	$C_{23}H_{24}F_3N_3O_4$	464.0	8.9	38
Example 607	271	$C_{21}H_{20}F_5N_3O_2$	442.0	6.1	28
Example 608	272	$C_{21}H_{22}F_3N_3O_3$	422.0	13.6	59
Example 609	273	$C_{22}H_{21}F_3N_4O_2$	431.0	12.6	59
Example 610	274	$C_{22}H_{21}F_3N_4O_2$	431.0	7.7	36
Example 611	275	$C_{22}H_{21}F_3N_4O_2$	431.0	12.7	59
Example 612	276	$C_{21}H_{20}F_5N_3O_2$	442.0	11.7	53
Example 613	277	$C_{27}H_{26}F_3N_3O_2$	482.0	9.5	39
Example 614	278	$C_{23}H_{24}F_3N_3O_4$	464.0	13.0	56
Example 615	279	$C_{22}H_{21}F_6N_3O_3$	490.0	10.4	42
Example 616	280	$C_{22}H_{21}F_6N_3O_3$	490.0	12.0	49
Example 617	281	$C_{22}H_{22}F_3N_3O_4$	450.0	4.9	22
Example 618	282	$C_{25}H_{30}F_3N_3O_2$	462.0	12.0	52
Example 619	283	$C_{20}H_{23}F_3N_4O_3$	425.0	8.1	38
Example 620	284	$C_{27}H_{25}ClF_3N_3O_2$	516.0	4.8	19
Example 621	285	$C_{21}H_{22}F_3N_3O_2$	406.0	4.8	24
Example 622	286	$C_{21}H_{21}F_4N_3O_2$	424.0	4.5	21
Example 623	287	$C_{21}H_{21}ClF_3N_3O_2$	440.0	5.8	26
Example 624	288	$C_{21}H_{20}Cl_2F_3N_3O_2$	474.0	8.1	34

Example 625	289	$C_{21}H_{20}Cl_2F_3N_3O_2$	474.0	8.0	34
Example 626	290	$C_{22}H_{24}F_3N_3O_2$	420.0	6.0	29
Example 627	291	$C_{21}H_{21}F_4N_3O_2$	424.0	6.2	29
Example 628	292	$C_{21}H_{21}ClF_3N_3O_2$	440.0	4.5	20
Example 629	293	$C_{21}H_{20}Cl_2F_3N_3O_2$	474.0	5.1	22
Example 630	294	$C_{22}H_{24}CF_3N_3O_3$	436.0	4.2	19
Example 631	295	$C_{22}H_{21}ClF_6N_3O_2$	474.0	6.0	25
Example 632	296	$C_{22}H_{24}F_3N_3O_2$	420.0	4.3	21
Example 633	297	$C_{21}H_{21}F_4N_3O_2$	424.0	8.2	39
Example 634	298	$C_{22}H_{24}F_3N_3O_3$	436.0	12.2	56
Example 635	299	$C_{22}H_{24}F_3N_3O_2$	420.0	8.1	39
Example 636	300	$C_{21}H_{20}ClF_3N_4O_4$	485.0	13.7	57
Example 637	301	$C_{21}H_{21}F_3N_4O_4$	451.0	15.1	67
Example 638	302	$C_{21}H_{21}F_3N_4O_4$	451.0	16.6	74
Example 639	303	$C_{22}H_{21}F_6N_3O_2$	474.0	12.6	53
Example 640	304	$C_{24}H_{26}F_3N_3O_4$	478.0	14.5	61
Example 641	305	$C_{22}H_{23}ClF_3N_3O_2$	420.0	8.4	37
Example 642	306	$C_{21}H_{20}Cl_2F_3N_3O_2$	474.0	13.5	57
Example 643	307	$C_{22}H_{21}ClF_6N_3O_2$	474.0	3.7	16
Example 644	308	$C_{21}H_{21}BrF_3N_3O_2$	484.0	7.2	30
Example 645	309	$C_{21}H_{21}BrF_3N_3O_2$	484.0	6.7	28
Example 646	310	$C_{27}H_{26}F_3N_3O_3$	498.0	4.2	17
Example 647	311	$C_{21}H_{21}BrF_3N_3O_2$	484.0	6.3	26
Example 648	312	$C_{22}H_{22}F_3N_3O_4$	450.0	2.4	11
Example 649	313	$C_{22}H_{24}F_3N_3O_3$	436.0	1.9	9
Example 650	314	$C_{23}H_{25}F_3N_4O_3$	463.0	5.0	22
Example 651	315	$C_{22}H_{24}F_3N_3O_4S$	484.0	2.5	10
Example 652	316	$C_{23}H_{24}F_3N_3O_4$	464.0	3.3	14
Example 653	317	$C_{21}H_{20}F_5N_3O_2$	442.0	4.5	20
Example 654	318	$C_{21}H_{22}F_3N_3O_3$	422.0	7.9	34
Example 655	319	$C_{22}H_{21}F_3N_4O_2$	431.0	6.5	30
Example 656	320	$C_{22}H_{21}F_3N_4O_2$	431.0	14.2	66
Example 657	321	$C_{22}H_{21}F_3N_4O_2$	431.0	14.9	69
Example 658	322	$C_{21}H_{20}F_5N_3O_2$	442.0	13.6	62
Example 659	323	$C_{27}H_{26}F_3N_3O_2$	482.0	3.9	16
Example 660	324	$C_{23}H_{24}F_3N_3O_4$	464.0	15.2	66
Example 661	325	$C_{22}H_{21}F_6N_3O_3$	490.0	16.1	66
Example 662	326	$C_{22}H_{21}F_6N_3O_3$	490.0	13.6	56
Example 663	327	$C_{22}H_{22}F_3N_3O_4$	450.0	5.4	24
Example 664	328	$C_{25}H_{30}F_3N_3O_2$	462.0	10.9	47

Example 665	329	$C_{20}H_{23}F_3N_4O_3$	425.0	12.0	57
Example 666	986	C27 H25 Cl F3 N3 O2	516.0	1.5	6
Example 667	1118	C28 H27 F3 N4 O3	525	21.5	62
Example 668	1119	C22 H24 F3 N3 O2 S	452	16.9	57
Example 669	1120	C23 H26 F3 N3 O4	466	20.5	67
Example 670	1121	C22 H23 F3 N4 O4	465	16.8	55
Example 671	1122	C28 H36 F3 N3 O2	504	21.0	63
Example 672	1123	C25 H23 Br F3 N3 O2	534	26.6	75
Example 673	1124	C19 H19 F3 N4 O5	441	21.3	73
Example 674	1133	C23 H26 F3 N3 O4	467	33.6	84
Example 675	1134	C24 H28 F3 N3 O5	496	34.8	82
Example 676	1135	C22 H21 F3 N4 O6	495	32.6	77
Example 677	1136	C23 H24 F3 N3 O5	480	36.6	89
Example 678	1137	C22 H21 Br F3 N3 O4	529	30.8	69
Example 679	1138	C24 H26 F3 N3 O2	446	32.7	86
Example 680	1139	C22 H24 F3 N3 O2	420	18.6	51
Example 681	1140	C21 H20 F3 N5 O6	496	20.5	49
Example 682	1141	C25 H24 F3 N3 O2	456	22.5	58
Example 683	1142	C25 H24 F3 N3 O2	456	21.6	55
Example 684	1143	C35 H34 F3 N3 O4	618	27.3	53
Example 685	1144	C23 H26 F3 N3 O4	466	25.5	64
Example 686	1145	C23 H25 F3 N4 O6	511	38.0	88
Example 687	1146	C28 H28 F3 N3 O3	512	38.3	89
Example 688	1147	C23 H25 F3 N4 O3	463	27.1	62
Example 689	1148	C27 H26 F3 N3 O2	482	22.4	57
Example 690	1161	C22 H24 F3 N3 O4	452	13.5	58
Example 691	1162	C24 H28 F3 N3 O3	464	16.7	70
Example 692	1163	C22 H23 F4 N3 O3	454	15.8	68
Example 693	1164	C23 H26 F3 N3 O3	450	15.7	68
Example 694	1165	C23 H24 F3 N3 O4	464	16.3	68
Example 695	1166	C22 H23 Br F3 N3 O3	513	15.0	57
Example 696	1168	C17 H17 Cl F3 N5 O2 S	448	6.9*	23
Example 697	1169	C20 H22 F3 N5 O3 S	470	1.7*	6
Example 698	1170	C22 H22 F3 N5 O2	446	2.3*	8
Example 699	1286	C26 H33 F3 N4 O3	507	25.3*	51
Example 700	1287	C21 H20 F3 N5 O6	496	4.0*	8
Example 701	1288	C22 H24 F3 N3 O4	452	3.6*	13
Example 702	1298	C23 H25 Br F3 N3 O4	544	28.4	quant
Example 703	1299	C24 H28 F3 N3 O5	496	1.4	6
Example 704	1300	C23 H26 F3 N3 O4	466	7.3	33

Example 705	1301	C24 H28 F3 N3 O5	496	12.6	53
Example 706	1302	C24 H28 F3 N3 O3	464	24.5	quant
Example 707	1303	C23 H25 Br F3 N3 O4	544	22.2	86
Example 708	1304	C29 H30 F3 N3 O4	542	28.6	quant
Example 709	1305	C26 H26 F3 N3 O3	486	35.4	quant
Example 710	1306	C24 H28 F3 N3 O4	480	8.1	35
Example 711	1307	C23 H26 F3 N3 O5	482	27.9	quant
Example 712	1308	C23 H24 F3 N3 O3	448	5.9	28
Example 713	1309	C23 H25 F3 I N3 O4	592	24.0	85
Example 714	1310	C22 H24 F3 N3 O4	452	3.4	16
Example 715	1311	C22 H22 F3 N3 O4	450	3.4	16
Example 716	1312	C21 H21 F3 I N3 O2	532	18.1	72
Example 717	1313	C21 H21 Br F3 N3 O2	484	17.4	76
Example 718	1314	C19 H19 F3 N4 O4 S	457	16.8	77
Example 719	1315	C20 H22 F3 N3 O3	410	13.6	70
Example 720	1316	C22 H20 Cl F6 N3 O2	508	18.6	77
Example 721	1317	C21 H20 Cl F3 N4 O4	485	17.0	74
Example 722	1318	C21 H20 Cl F4 N3 O2	458	17.0	78
Example 723	1319	C21 H20 Cl F4 N3 O2	458	17.6	81
Example 724	1320	C21 H20 Br F4 N3 O2	502	18.5	77
Example 725	1390	C26 H32 F3 N3 O2	476	16.1	51
Example 726	1391	C23 H26 F3 N3 O2	434	20.0	76
Example 727	1392	C22 H23 Cl F3 N3 O2	454	20.0	67
Example 728	1393	C23 H26 F3 N3 O2	434	20.1	70
Example 729	1394	C22 H23 F3 N4 O4	465	18.4	60
Example 730	1395	C23 H24 F3 N3 O2	432	21.4	75
Example 731	1396	C26 H26 F3 N3 O2	470	20.4	66
Example 732	1397	C21 H20 Br2 F3 N3 O2	562	14.5	54
Example 733	1398	C22 H22 Cl2 F3 N3 O2	488	10.8	47
Example 734	1399	C22 H22 Cl2 F3 N3 O2	488	9.4	40
Example 735	1400	C22 H23 Cl F3 N3 O2	454	19.1	88
Example 736	1614	C22 H21 F6 N3 S	506.0	24.2	96
Example 737	2050	C20 H22 F3 N3 O2 S	426	6.0	30
Example 738	2051	C21 H23 F3 N4 O2	421	6.5	32

*Yield of TFA salt.

Examples 739-748.

The compounds of this invention were synthesized pursuant to methods of Example 738 using the corresponding reactant respectively. Preparative TLC,

if needed, afforded the desired material. The ESI/MS data and yields are summarized in Table 9.

Table 9

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 739	1650	C24 H28 F3 N3 O2	448.0	20.4	91
Example 740	1706	C23 H25 F3 N4 O3	463.2	3.7	11
Example 741	1707	C22 H25 F3 N4 O2 S	467.0	10.3	29
Example 742	1708	C23 H27 F3 N4 O2	449.2	11.4	34
Example 743	1709	C24 H29 F3 N4 O2	463.2	15.2	44
Example 744	1775	C22 H25 F3 N4 O4	467.2	9.2	26.3
Example 745	1776	C22 H25 F3 N4 O4	467.2	8.9	25.4
Example 746	1787	C24 H29 F3 N4 O2	463.2	5.6	16.1
Example 747	1802	C23 H27 F3 N4 O4	481.2	11.7	32.5
Example 748	1803	C22 H25 F3 N4 O3	451.2	9.6	28.4

Example 749: Preparation of (*R*)-3-[{*N*-(2-Amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-(3-hydroxy-4-methoxybenzyl)pyrrolidine (Compound No. 1896).

To a mixture of (*R*)-3-[*N*-{2-(tert-butoxycarbonylamino)-5-(trifluoromethoxy)benzoyl}glycyl]aminopyrrolidine (0.050 mmol), 3-hydroxy-4-methoxybenzaldehyde (0.060 mmol), $NaBH_3CN$ (0.15 mmol), and methanol (1.3 mL) was added acetic acid (0.050 mL). The reaction mixture was stirred at 60 °C for 8 h. The mixture was cooled to room temperature, loaded onto Varian™ SCX column, and washed with CH_3OH (10 mL). Product was eluted off using 2 N NH_3 in CH_3OH (5 mL) and concentrated. To the resulting material was added 4 N HCl in 1,4-dioxane and the solution was stirred overnight at room temperature. Concentration and preparative TLC gave (*R*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-(3-hydroxy-4-methoxybenzyl)pyrrolidine (Compound No. **1896**) (9.1 mg, 38%): The purity was determined by RPLC/MS (93%); ESI/MS m/e 483 (M^{+}+H, $C_{22}H_{25}F_3N_4O_5$).

Examples 750-757.

The compounds of this invention were synthesized pursuant to methods of Example 749 using the corresponding reactant respectively. The ESI/MS data and yields are summarized in Table 10.

Table 10

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 750	1897	C22 H25 F3 N4 O3 S	483	22.7	94.1
Example 751	1898	C23 H27 F3 N4 O3	465	12.2	52.5
Example 752	1899	C24 H29 F3 N4 O3	479	14.4	60.2
Example 753	1900	C22 H25 F3 N4 O5	483	2.6	10.8
Example 754	1901	C24 H29 F3 N4 O3	479	14.5	60.6
Example 755	1902	C23 H25 F3 N4 O4	479	12.0	50.2
Example 756	1915	C23 H27 F3 N4 O5	467.2	2.5	6.7
Example 757	1916	C22 H25 F3 N4 O4	467.2	3.1	8.9

Example 758: Preparation of (*R*)-3-[{*N*-(2-Amino-5-(trifluoromethyl)benzoyl)glycyl}amino]-1-(4-vinylbenzyl)pyrrolidine (Compound No. 1701).

A mixture of (*R*)-3-[{*N*-(2-amino-5-(trifluoromethyl)benzoyl)glycyl}amino]pyrrolidine (0.050 mmol), 4-vinylbenzyl chloride (9.9 mg, 0.065 mmol), piperidinomethylpolystyrene (60 mg), acetonitrile (1.0 mL) and chloroform (0.30 mL) was stirred at 50 °C for 12 h. The reaction mixture was cooled, loaded onto Varian™ SCX column and washed with CH_3OH (15 mL). Product was eluted using 2 N NH_3 in CH_3OH (5 mL) and concentrated to afford (*R*)-3-[{*N*-(2-amino-5-(trifluoromethyl)benzoyl)glycyl}amino]-1-(4-vinylbenzyl)pyrrolidine (Compound No. **1701**) (19.6 mg, 88%): The purity was determined by RPLC/MS (92%); ESI/MS m/e 547.2 (M^{+}+H, $C_{23}H_{25}ClF_3N_4O_2$).

Examples 759-762

The compounds of this invention were synthesized pursuant to methods of Example 758 using the corresponding reactant respectively. Preparative TLC, if needed, afforded the desired material. The ESI/MS data and yields are summarized in Table 11.

Table 11

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 759	1702	C22 H25 F3 N4 O3	451.2	5.3	24
Example 760	1703	C22 H23 F3 N4 O4	465.2	5.0	22
Example 761	1704	C21 H23 F3 N4 O3	437.2	20.9	96
Example 762	1705	C21 H21 Cl2 F3 N4 O2	489.2	9.3	38

Example 763: Preparation of (*R*)-3-[{*N*-(2-Amino-5-(trifluoromethoxy)benzoyl)glycyl}amino]-1-(2,4-dichlorobenzyl)pyrrolidine (Compound No. 1905).

A mixture of (*R*)-3-[{*N*-(2-amino-5-(trifluoromethoxy)benzoyl)glycyl}amino]pyrrolidine (0.050 mmol), 2,4-dichlorobenzyl chloride (0.060 mmol), piperidinomethylpolystyrene (60 mg), acetonitrile (0.8 mL) and chloroform (0.5 mL) was stirred at 60 °C for 12 h. The reaction mixture was cooled, loaded onto Varian™ SCX column and washed with 50% $CHCl_3/CH_3OH$ (10 mL) and CH_3OH (10 mL). Product was eluted using 2 N NH_3 in CH_3OH (5 mL) and concentrated. To the resulting material was added 4 N HCl in 1,4-dioxane (2 mL), and the solution was stirred overnight at room temperature. Concentration and preparative TLC afforded (*R*)-3-[{*N*-(2-amino-5-(trifluoromethoxy)benzoyl)glycyl}amino]-1-(2,4-dichlorobenzyl)pyrrolidine (Compound No. **1905**) (17.6 mg, 70%): The purity was determined by RPLC/MS (93%); ESI/MS m/e 505 (M^++H, $C_{21}H_{21}Cl_2F_3N_4O_3$).

Examples 764-770

The compounds of this invention were synthesized pursuant to methods of Example 763 using the corresponding reactant respectively. The ESI/MS data and yields are summarized in Table 12.

Table 12

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 764	1906	C22 H23 F3 N4 O5	481	9.4	39.1
Example 765	1907	C21 H23 F3 N4 O4	453	7.5	33.2
Example 766	1908	C22 H25 F3 N4 O4	467	7.7	33.0
Example 767	2180	C22 H24 Cl F3 N4 O2	469	1.3	26
Example 768	2181	C23 H25 F3 N6 O3	491	4.3	52
Example 769	2182	C19 H22 F3 N5 O2 S	442	7.0	51
Example 770	1909	C23 H25 F3 N4 O3	463	8.7	37.6

Example 771: Preparation of (*R*)-3-[{*N*-(2-Amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-(2-amino-4-chlorobenzyl)pyrrolidine (Compound No. 1921).

A mixture of (*R*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]pyrrolidine (0.050 mmol), 4-chloro-2-

nitrobenzyl chloride (0.050 mmol), piperidinomethylpolystyrene (60 mg), acetonitrile (1.0 mL) and chloroform (0.7 mL) was stirred overnight at 50 °C. The reaction mixture was cooled, loaded onto Varian™ SCX column and washed with 50% $CHCl_3/CH_3OH$ (10 mL) and CH_3OH (10 mL). Product was eluted using 2 N NH_3 in CH_3OH (5 mL) and concentrated. To the resulting material was added ethanol (3 mL) and 10% Pd-C (15 mg), and the mixture was stirred under H_2 at room temperature for 1.5 h. Filtration, concentration, and preparative TLC afforded (*R*)-3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-(2-amino-4-chlorobenzyl)pyrrolidine (Compound No. **1921**) (2.2 mg, 6%): The purity was determined by RPLC/MS (81%); ESI/MS m/e 486.2 (M^{+}+H, $C_{21}H_{23}ClF_3N_5O_3$).

Example 772: Preparation of (*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-bromo-2-fluorobenzyl)pyrrolidine (Compound No. 2120).

To a mixture of (*R*)-3-[{*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine (0.050 mmol), 4-bromo-2-fluorobenzaldehyde (0.15 mmol), methanol (1.5 mL), and acetic acid (0.016 mL) was added $NaBH_3CN$ (0.25 mmol) in methanol (0.50 mL). The reaction mixture was stirred at 50 °C overnight. The mixture was cooled to room temperature, loaded onto Varian™ SCX column, and washed with CH_3OH (5 mL x 2). Product was eluted off using 2 N NH_3 in CH_3OH (5 mL) and concentrated. The residue was dissolved in methanol (0.25 mL) and 4 N HCl in dioxane (0.50 mL) was added. The solution was stirred at room temperature for 5 h and concentrated. The residue was dissolved in methanol, loaded onto Varian™ SCX column, and washed with CH_3OH (5 mL x 2). Product was eluted off using 2 N NH_3 in CH_3OH (5 mL) and concentrated. The resulting material was dissolved into ethyl acetate (0.5 mL), loaded onto Varian™ Si column, eluted off using ethyl acetate/methanol = 5:1 (6 mL), and concentrated to afford (*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-bromo-2-fluorobenzyl)pyrrolidine (Compound No. **2120**) (16.0 mg, 31%): The purity was determined by RPLC/MS (99%); ESI/MS m/e 517.0 (M^{+}+H, $C_{21}H_{21}BrF_4N_4O_2$).

Examples 773-793.

The compounds of this invention were synthesized pursuant to methods of Example 772 using the corresponding reactant respectively. The ESI/MS data and yields are summarized in Table 13.

Table 13

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 773	2083	C22 H24 Br F3 N4 O4	545.2	2.9	11
Example 774	2084	C23 H27 F3 N4 O5	497.2	5.1	21
Example 775	2085	C22 H25 F3 N4 O4	467.2	3.1	13
Example 776	2086	C21 H22 Cl F3 N4 O3	471.0	4.6	20
Example 777	2087	C23 H28 F3 N5 O2	464.2	5.6	24
Example 778	2088	C25 H32 F3 N5 O2	492.2	5.9	24
Example 779	2089	C21 H21 F5 N4 O2	457.2	4.5	20
Example 780	2090	C27 H27 F3 N4 O3	513.2	8.0	31
Example 781	2118	C21 H23 F3 N4 O4	453.1	2.7	12
Example 782	2119	C21 H23 F3 N4 O4	453.1	4.3	19
Example 783	2121	C22 H25 F3 N4 O4	467.0	1.2	2
Example 784	2122	C21 H21 Cl F4 N4 O2	472.9	13.1	28
Example 785	2123	C22 H22 F3 N5 O6	510.1	13.1	51
Example 786	2124	C21 H21 Cl F3 N5 O4	500.1	15.6	62
Example 787	2125	C22 H24 F3 N5 O5	496.0	16.0	65
Example 788	2126	C22 H24 F3 N5 O4	480.1	15.6	65
Example 789	2137	C22 H24 Cl F3 N4 O2	469.2	2.6	11
Example 790	2138	C26 H29 F3 N6 O2	515.3	25.1	98
Example 791	2139	C20 H24 Cl F3 N6 O2	473.2	25.0	98
Example 792	2149	C21 H22 F3 N5 O5	482.3	4.9	34
Example 793	2157	C22 H25 F3 N4 O3	451.2	15.5	70

Example 794: Preparation of (*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(2,4-dimethoxypyrimidin-5-ylmethyl)pyrrolidine (Compound No. 2175).

(*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine (17.2 mg, 0.04 mmol) was dissolved in THF (1 mL) and 2,4-dimethoxy-5-pyrimidine carboxaldehyde (6.7 mg, 0.04 mmol) was added followed by sodium triacetoxyborohydride (12.7 mg, 0.06 mmol) and glacial acetic acid (2.4 mg, 0.04 mmol). The mixture was stirred at room temperature for 24 h and evaporated. The residue was then dissolved in dichloromethane (1 mL) and washed with 1 N NaOH solution (1 mL). The organic phase was recovered and evaporated then treated with 25% trifluoroacetic acid in dichloromethane (1 mL) for 1 h at room temperature and evaporated. The residue was purified using LC/MS to afford (*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(2,4-dimethoxypyrimidin-5-ylmethyl)pyrrolidine (Compound No. **2175**) (18.6 mg, 78%): The purity was determined by RPLC/MS (98%); ESI/MS m/e 483 (M^{+}+H, $C_{21}H_{25}F_{3}N_{6}O_{4}$).

Examples 795-803.

The compounds of this invention were synthesized pursuant to methods of Example 794 using the corresponding reactant respectively. The ESI/MS data and yields are summarized in Table 14.

Table 14

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 795	2165	C18 H21 F3 N6 O2	411	2.0	27
Example 796	2166	C18 H20 F3 N5 O2 S	428	9.9	66
Example 797	2167	C24 H25 F3 N6 O2	487	15.1	73
Example 798	2169	C24 H29 F3 N4 O2	463	1.2	24
Example 799	2170	C26 H25 Cl F3 N5 O2	520	6.0	40
Example 800	2171	C19 H23 F3 N6 O2	425	16.8	88
Example 801	2174	C23 H24 Br F3 N4 O2 S2	591	5.3	53
Example 802	2178	C25 H28 F3 N5 O4	518	5.4	62
Example 803	2179	C25 H28 F3 N5 O3	502	6.3	60

Example 804: Preparation of (*R*)-1-(2-Amino-4,5-methylenedioxybenzyl)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine (Compound No. 2127).

A mixture of (*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4,5-methylenedioxy-2-nitrobenzyl)pyrrolidine (30.5 mg), 10% Pd-activated carbone (6 mg), and methanol (3 mL) was stirred under a hydrogen atmosphere at room temperature for 10 h. The Pd catalyst was filtered off through Celite, and the filtrate was concentrated. Solid phase extraction (Bond Elut™ SI, 20% methanol/AcOEt) afforded (*R*)-1-(2-amino-4,5-methylenedioxybenzyl)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine (Compound No. **2127**) (21.9 mg, 76%): The purity was determined by RPLC/MS (95%); ESI/MS m/e 480.1 (M^++H, $C_{22}H_{24}F_3N_5O_4$).

Examples 805 and 806.

The compounds of this invention were synthesized pursuant to methods of Example 804 using the corresponding reactant respectively. The ESI/MS data and yields are summarized in Table 15.

Table 15

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 805	2128	C22 H26 F3 N5 O3	466.0	8.6	30
Example 806	2129	C22 H26 F3 N5 O2	450.1	13.1	37

Example 807: Preparation of (*R*)-1-(3-Amino-4-chlorobenzyl)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine (Compound No. 2132).

A mixture of (*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-chloro-3-nitrobenzyl)pyrrolidine (32.6 mg), 10% Pd-activated carbone (8 mg), ethyl acetate (2.7 mL) and methanol (0.3 mL) was stirred under a hydrogen atmosphere at room temperature for 15 h. The Pd catalyst was filtered off, and the filtrate was concentrated. Solid phase extraction (Bond Elut™ SI, 20% methanol/AcOEt) afforded (*R*)-1-(3-amino-4-chlorobenzyl)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine (Compound No. **2132**) (10.5 mg, 34%): The purity was determined by RPLC/MS (84%); ESI/MS m/e 470.2 (M^++H, $C_{21}H_{23}ClF_3N_5O_2$).

Example 808: Preparation of (*R*)-1-(2-Amino-4,5-methylenedioxybenzyl)-3-[{*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine.

To a mixture of (*R*)-3-[{*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine (0.150 mmol), 4,5-methylenedioxy-2-nitrobenzaldehyde (0.45 mmol), methanol (4.5 mL), and acetic acid (0.048 mL) was added $NaBH_3CN$ (0.75 mmol) in methanol (1.50 mL). The reaction mixture was stirred at 50 °C overnight. The mixture was cooled to room temperature, loaded onto Varian™ SCX column, and washed with CH_3OH. Product was eluted off using 2 N NH_3 in CH_3OH and concentrated to afford (*R*)-3-[{*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4,5-methylenedioxy-2-nitrobenzyl)pyrrolidine.

A mixture of (*R*)-3-[{*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4,5-methylenedioxy-2-nitrobenzyl)pyrrolidine prepared above, 10% Pd-activated carbone (22 mg), and methanol (3.0 mL) was stirred under a hydrogen atmosphere at room temperature overnight. The Pd catalyst was filtered off, and the filtrate was concentrated to afford (*R*)-1-(2-amino-4,5-methylenedioxybenzyl)-3-[{*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine

(87.1 mg, quant.): Any remarkable by-products were not detected in TLC.

(*R*)-1-(3-Amino-4-methoxybenzyl)-3-[{*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine and (*R*)-1-(3-amino-4-methylbenzyl)-3-[{*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine were also synthesized pursuant to methods of Example 808 using the corresponding reactant respectively.

(*R*)-1-(3-Amino-4-methoxybenzyl)-3-[{*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine: 101 mg, quant.; Any remarkable by-products were not detected in TLC.

(*R*)-1-(3-amino-4-methylbenzyl)-3-[{*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine: 97.2 mg, quant.; Any remarkable by-products were not detected in TLC.

Example 809: Preparation of (*R*)-1-(3-Amino-4-chlorobenzyl)-3-[{*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine.

To a mixture of (*R*)-3-[{*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine (0.150 mmol), 4-chloro-3-nitrobenzaldehyde (0.45 mmol), methanol (4.5 mL), and acetic acid (0.048 mL) was added $NaBH_3CN$ (0.75 mmol) in methanol (1.50 mL). The reaction mixture was stirred at 50 °C overnight. The mixture was cooled to room temperature, loaded onto Varian™ SCX column, and washed with CH_3OH. Product was eluted off using 2 N NH_3 in CH_3OH and concentrated to afford (*R*)-3-[{*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-chloro-3-nitrobenzyl)pyrrolidine.

A mixture of (*R*)-3-[{*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-chloro-3-nitrobenzyl)pyrrolidine prepared above, 10% Pd-activated carbone (22 mg), ethyl acetate (2.7 mL) and methanol (0.3 mL) was stirred under a hydrogen atmosphere at room temperature for 15 h. The Pd catalyst was filtered off, and the filtrate was concentrated to afford (*R*)-1-(3-amino-4-chlorobenzyl)-3-[{*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine (89.7 mg, quant.): Any remarkable by-products were not detected in TLC.

Example 810: Preparation of (*R*)-1-(3-Amino-4-hydroxybenzyl)3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine (Compound No. 2187).

A solution of (*R*)-1-(3-amino-4-hydroxybenzyl)-3-[{*N*-(2-(*tert*-

butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine (20 mg), prepared pursuant to methods of Example 808, in 4 N HCl in dioxane (2.0 mL) was stirred at room temperature overnight. After the solution was concentrated, the residue was dissolved in methanol, loaded onto Varian™ SCX column, washed with CH_3OH, and eluted off using 2 N NH_3 in CH_3OH. Concentration and preparative TLC (SiO_2, AcOEt/MeOH = 4:1) afforded (*R*)-1-(3-amino-4-hydroxybenzyl)3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine (Compound No. **2187**) (9.6 mg, 59%): The purity was determined by RPLC/MS (86%); ESI/MS m/e 452.3 (M^++H, $C_{21}H_{24}F_3N_5O_3$).

Example 811: Preparation of (*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-chloro-3-(dimethylamino)benzyl}pyrrolidine (Compound No. 2133).

To a mixture of (*R*)-1-(3-amino-4-chlorobenzyl)-3-[{*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine (44.9 mg), methanol (0.95 mL), acetic acid (0.05 mL), and 37% aqueous HCHO solution (0.15 mL) was added $NaBH_3CN$ (38 mg). The reaction mixture was stirred at 50 °C overnight. The mixture was cooled to room temperature and evaporated. To the residue was added 2 N aqueous NaOH solution and ethyl acetate, the organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried and concentrated, and the residue was loaded onto Varian™ SCX column and washed with CH_3OH. Product was eluted off using 2 N NH_3 in CH_3OH and concentrated. The residue was dissolved in 50% conc. HCl/dioxane and the solution was stirred at room temperature for 1 h. The reaction mixture was adjusted to pH 10 with 5 N aqueous NaOH solution and extracted with ethyl acetate (2 times). The combined extracts were dried over Na_2SO_4, filtered, and evaporated. Preparative TLC (SiO_2, 20% MeOH/AcOEt) gave (*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-chloro-3-(dimethylamino)benzyl}pyrrolidine (Compound No. **2133**). (10.9 mg, 28%): The purity was determined by RPLC/MS (95%); ESI/MS m/e 498.3 (M^++H, $C_{23}H_{27}ClF_3N_5O_2$).

Examples 812-814.

The compounds of this invention were synthesized pursuant to methods of Example 811 using the corresponding reactant respectively. The ESI/MS data and yields are summarized in Table 16.

Table 16

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 812	2134	$C_{24}H_{28}F_3N_5O_4$	508.4	19.0	50
Example 813	2135	$C_{24}H_{30}F_3N_5O_3$	494.4	21.8	50
Example 814	2136	$C_{24}H_{30}F_3N_5O_2$	478.4	29.2	69

Example 815: Preparation of (*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(3-methylamino-4-hydroxybenzyl)pyrrolidine (Compound No. 2158).

To a mixture of (*R*)-1-(3-amino-4-hydroxybenzyl)-3-[{*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine (27.3 mg, 0.049 mmol), 37% HCHO solution (4.0 mg, 0.049 mmol), acetic acid (0.10 mL) and methanol (1.3 mL) was added $NaBH_3CN$ (9.2 mg) in methanol (0.2 mL). The reaction mixture was stirred at 60 °C overnight. The mixture was cooled to room temperature, loaded onto Varian™ SCX column, and washed with CH_3OH (5 mL x 2). Product was eluted off using 2 N NH_3 in CH_3OH (8 mL) and concentrated.

The resulting material was dissolved in methanol (1 mL) and 4 N HCl in dioxane (1.0 mL) was added. The solution was stirred at room temperature for 3 h. After the solution was concentrated, the residue was dissolved in methanol (1 mL), loaded onto Varian™ SCX column, washed with CH_3OH (5 mL x 2), and eluted off using 2 N NH_3 in CH_3OH (8 mL). Concentration and preparative TLC (SiO_2) afforded (*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(3-methylamino-4-hydroxybenzyl)pyrrolidine (Compound No. **2158**) (4.3 mg, 19%): The purity was determined by RPLC/MS (71%); ESI/MS m/e 480.3 (M^++H, $C_{22}H_{26}F_3N_5O_3$).

Example 816: Preparation of (R)-1-(3-Acetylamino-4-methoxybenzyl)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine (Compound No. 2152).

To a solution of (*R*)-1-(3-amino-4-methoxybenzyl)-3-[{*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine (50.5 mg)in pyridine (1 mL) was added acetic anhydride (1 mL). The reaction mixture was stirred at room temperature overnight and methanol was added. The mixture was evaporated, and 1 N NaOH solution was added. The mixture was extracted with ethyl acetate and the organic layer was concentrated. Preparative TLC gave (*R*)-1-(3-acetylamino-4-methoxybenzyl)-3-[{*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine.

The resulting (*R*)-1-(3-acetylamino-4-methoxybenzyl)-3-[{*N*-(2-(*tert*-

butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine was dissolved in 50% 6 N hydrochloric acid in dioxane and the solution was stirred at room temperature for 2 h. The mixture was adjusted to pH 10 with 5 M NaOH solution, and extracted with ethyl acetate. The organic layer was evaporated and preparative TLC (SiO_2, AcOEt/MeOH = 4:1) afforded (*R*)-1-(3-acetylamino-4-methoxybenzyl)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine (Compound No. **2152**) (3.7 mg, 8%): The purity was determined by RPLC/MS (100%); ESI/MS m/e 508.3 (M^++H, $C_{24}H_{28}F_3N_5O_4$).

Examples 817-819.

The compounds of this invention were synthesized pursuant to methods of Example 816 using the corresponding reactants respectively. The ESI/MS data and yields are summarized in Table 17.

Table 17

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 817	2150	C23H25ClF3N5O3	512.3	3.8	9
Example 818	2151	C24H26F3N5O5	522.2	3.1	8
Example 819	2153	C24H28F3N5O3	492.3	4.3	10

Example 820: Preparation of (*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(benz[d]oxazol-5-yl)pyrrolidine (Compound No. 2189).

A solution of (R)-1-(3-amino-4-hydroxybenzyl)-3-[{*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine (20 mg), prepared pursuant to methods of Example 808, in THF (2 mL) was treated with triethyl orthoformate (0.020 mL, 3.3 eq) and pyridinium *p*-toluenesulphonate (1.2 mg, 0.4 eq). The reaction mixture was stirred overnight under reflux. After cooling to room temperature, the mixture was concentrated. The residue was dissolved in AcOEt, loaded onto BondElut™ Si column, eluted off using ethyl acetate/methanol = 4/1, and concentrated.

The resulting material was dissolved into AcOEt (1.5 mL), and 4 N HCl in dioxane (0.5 mL) was added. The solution was stirred at room temperature overnight, adjusted to pH 10 with 5 M NaOH aqueous solution, and extracted with AcOEt. The extract was concentrated and purified by PTLC (SiO_2, AcOEt/MeOH =

4:1) to afford (*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(benz[d]oxazol-5-yl)pyrrolidine (Compound No. **2189**) (0.5 mg, 3%): The purity was determined by RPLC/MS (97%); ESI/MS m/e 462.3 (M^{+}+H, $C_{22}H_{22}F_3N_5O_3$).

Example 821: Preparation of (*R*)-3-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(benzo[c]thiadiazol-5-yl)pyrrolidine (Compound No. 2183).

To a mixture of 5-(hydroxymethyl)benzo[c]thiadiazole (8.3 mg, 0.050 mmol), (piperidinomethyl)polystyrene (86 mg), and chloroform (1 mL) was added methanesulfonyl chloride (0.0042 mL) and the mixture was stirred at room temperature for 1.5 h. Acetonitrile (1 mL) and (*R*)-3-[{*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine (0.060 mmol) was added and the reaction mixture was stirred at 50 °C for 3 h. After cooling to room temperature, phenyl isocyanate (30 mg) was added, and the mixture was stirred at room temperature for 1 h, loaded onto Varian™ SCX column and washed with CH_3OH (5 mL) and $CHCl_3$ (5 mL). Product was eluted using 2 N NH_3 in CH_3OH (3 mL) and concentrated.

The resulting material was dissolved into dichloromethane (1 mL), and 1 M chlorotrimethylsilane and 1 M phenol in dichloromethane (1 mL) was added. The solution was stirred at room temperature for 5 h, loaded onto Varian™ SCX column and washed with CH_3OH and dichloromethane. Product was eluted using 2 N NH_3 in CH_3OH and concentrated. Preparative TLC (SiO_2, AcOEt/MeOH = 3:1) afforded (*R*)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(benzo[c]thiadiazol-5-yl)pyrrolidine (Compound No. **2183**) (11.5 mg, 48%): The purity was determined by RPLC/MS (86%); ESI/MS m/e 479.2 (M^{+}+H, $C_{21}H_{21}F_3N_6O_2S$).

Reference Example 6: Preparation of 4-[{*N*-(1-(9-fuluorenylmethoxycarbonyl)pyrrolidin-3-yl)carbamoylmethyl}aminomethyl]-3-methoxyphenyloxymethyl-polystyrene.

To a solution of (*R*)-1-(9-fuluorenylmethoxycarbonyl)-3-glycylamino-pyrrolidine hydrochloride (4.38 g, 10 mmol) in DMF (65 mL) were added acetic acid (0.3 mL), sodium triacetoxyborohydride (1.92 g), and 4-formyl-3-(methoxyphenyloxymethyl)-polystyrene (1 mmol/g, 200 g). The mixture was shaken for 2 h and filtered. The resin was washed with MeOH, DMF, CH_2Cl_2, and methanol, and dried to afford the desired material (2.73 g).

Examples 822-912: General Procedure for Solid-Phase Synthesis of 3-Aminopyrrolidines.

To a mixture of the corresponding acid (1.6 mmol), HBTU (1.6 mmol), and DMF (6 mL) was added diisopropylethylamine (3.6 mmol), and the mixture was shaken for 2 min. 4-[{*N*-(1-(9-fuluorenylmethoxycarbonyl)pyrrolidin-3-yl)carbamoylmethyl}aminomethyl]-3-methoxyphenyloxymethyl-polystyrene (400 mg, 0.4 mmol) was added and the mixture was shaken for 1 h and filtered. The resin was rinsed with DMF and CH_2Cl_2, and dried.

A mixture of the resulting resin, piperidine (3.2 mL), and DMF (12.8 mL) was shaken for 10 min and filtered. The resin was washed with DMF and CH_2Cl_2, and dried.

To the dry resin (0.05 mmol) was added a mixture of $NaBH(OAc)_3$ (0.25 mmol), AcOH (0.025 mL) and DMF (1 mL). The corresponding aldehyde (2.5 mmol) was added, and the mixture was shaken for 2 h, then filtered and washed with CH_3OH, 10% diisopropylethylamine in DMF, DMF, CH_2Cl_2, and CH_3OH. A mixture of the resin, water (0.050 mL), and trifluoroacetic acid (0.95 mL) was shaken for 1 h and filtered. The resin was washed with CH_2Cl_2 and CH_3OH. The filtrate and washings were combined and concentrated. The crude material was loaded onto Varian™ SCX column and washed with CH_3OH (15 mL). Product was eluted using 2 N NH_3 in CH_3OH (5 mL) and concentrated. Preparative TLC or HPLC, if needed, afforded the desired material. The ESI/MS data and yields are summarized in Table 18.

Table 18

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 822	1805	C21 H21 Br F3 N3 O2 S	516	13.3	76
Example 823	1806	C22 H24 F3 N3 O3 S	468	12.8	81
Example 824	1807	C22 H24 F3 N3 O4 S	484	13.7	83
Example 825	1808	C22 H24 F3 N3 O4 S	484	14.9	91
Example 826	1809	C21 H22 F3 N3 O3 S	454	12.9	84
Example 827	1810	C22 H22 F3 N3 O4 S	482	12.9	79
Example 828	1811	C24 H26 F3 N3 O2 S	478	12.9	79
Example 829	1812	C22 H24 F3 N3 O2 S2	484	5.3	32
Example 830	1813	C23 H26 F3 N3 O2 S	466	12.8	81
Example 831	1814	C23 H24 F3 N3 O3 S	480	9.7	59
Example 832	1815	C23 H26 F3 N3 O2 S	466	12.7	80
Example 833	1816	C24 H28 F3 N3 O2 S	480	14.4	88
Example 834	1817	C25 H30 F3 N3 O2 S	494	14.1	84
Example 835	1818	C21 H22 Br F2 N3 O3	482	13.4	82
Example 836	1819	C22 H25 F2 N3 O4	434	11.7	79

Example 837	1820	C22 H25 F2 N3 O5	450	11.8	77
Example 838	1821	C22 H25 F2 N3 O5	450	13.3	87
Example 839	1822	C21 H23 F2 N3 O4	420	11.9	83
Example 840	1823	C22 H23 F2 N3 O5	448	11.9	78
Example 841	1824	C24 H27 F2 N3 O3	444	9.1	60
Example 842	1825	C22 H25 F2 N3 O3 S	450	11.3	74
Example 843	1826	C23 H27 F2 N3 O3	432	10.8	74
Example 844	1827	C23 H25 F2 N3 O4	446	12.7	84
Example 845	1828	C23 H27 F2 N3 O3	432	11.7	80
Example 846	1829	C24 H29 F2 N3 O3	446	14.3	94
Example 847	1830	C24 H29 F2 N3 O3	446	10.0	66
Example 848	1831	C22 H28 Br N3 O3	462	4.8	31
Example 849	1832	C23 H31 N3 O4	414	10.4	74
Example 850	1833	C23 H31 N3 O5	430	12.1	83
Example 851	1834	C23 H31 N3 O5	430	12.0	82
Example 852	1835	C22 H29 N3 O4	400	7.9	58
Example 853	1836	C23 H29 N3 O5	428	11.1	76
Example 854	1837	C25 H33 N3 O3	424	13.3	92
Example 855	1838	C23 H31 N3 O3 S	430	8.7	60
Example 856	1839	C24 H33 N3 O3	412	11.3	81
Example 857	1840	C24 H31 N3 O4	426	12.9	89
Example 858	1841	C24 H33 N3 O3	413	12.8	91
Example 859	1842	C25 H35 N3 O3	426	8.7	60
Example 860	1843	C25 H35 N3 O3	426	12.2	84
Example 861	1844	C26 H37 N3 O3	440	11.3	76
Example 862	1845	C31 H37 Br N4 O2	577	6.4	30
Example 863	1846	C23 H28 F3 N3 O2 S	480	12.8	81
Example 864	1847	C25 H31 F2 N3 O3	460	12.2	78
Example 865	1848	C27 H29 N3 O4	460	6.1	39
Example 866	1849	C29 H31 N3 O2	454	15.1	98
Example 867	1850	C28 H31 N3 O2	442	12.7	85
Example 868	1851	C28 H31 N3 O2	442	14.3	95
Example 869	1852	C28 H29 N3 O3	456	3.4	22
Example 870	1853	C27 H29 N3 O6 S	524	15.4	87
Example 871	1854	C29 H31 N3 O4 S	518	15.8	90
Example 872	1855	C28 H31 N3 O4 S	506	17.0	99
Example 873	1856	C28 H31 N3 O4 S	506	3.0	17
Example 874	1857	C28 H29 N3 O5 S	520	10.0	57
Example 875	1858	C20 H22 Br2 N4 O2	511	9.3*	37
Example 876	1859	C21 H25 Br N4 O3	461	6.7*	29

Example 877	1860	C21 H25 Br N4 O4	477	9.5*	40
Example 878	1861	C21 H25 Br N4 O4	477	10.0*	42
Example 879	1862	C20 H23 Br N4 O3	447	7.8*	34
Example 880	1863	C21 H23 Br N4 O4	475	3.4*	14
Example 881	1864	C21 H25 Br N4 O2 S	477	3.9*	16
Example 882	1865	C22 H25 Br N4 O3	473	6.4*	27
Example 883	1866	C23 H29 Br N4 O2	472	7.0*	29
Example 884	1867	C23 H29 Br N4 O2	473	7.6*	32
Example 885	1868	C24 H31 Br N4 O2	487	9.1*	37
Example 886	1869	C20 H22 Br I N4 O2	557	8.9*	33
Example 887	1870	C21 H25 I N4 O3	509	9.2*	37
Example 888	1871	C21 H25 I N4 O4	525	6.3*	25
Example 889	1872	C21 H25 I N4 O4	525	5.9*	23
Example 890	1873	C20 H23 I N4 O3	495	7.7*	31
Example 891	1874	C21 H23 I N4 O4	523	8.2*	32
Example 892	1875	C23 H27 I N4 O2	519	6.7*	26
Example 893	1876	C21 H25 I N4 O2	525	4.3*	17
Example 894	1877	C22 H27 I N4 O2	507	7.9*	32
Example 895	1878	C22 H25 I N4 O3	521	8.4*	33
Example 896	1879	C23 H29 I N4 O2	521	8.2*	32
Example 897	1880	C23 H29 I N4 O2	521	8.1*	32
Example 898	1881	C24 H31 I N4 O2	535	8.6*	33
Example 899	1882	C20 H22 Br N5 O4	476	5.3*	22
Example 900	1883	C21 H25 N5 O5	428	5.7*	26
Example 901	1884	C21 H25 N5 O6	444	8.2*	36
Example 902	1885	C21 H25 N5 O6	444	5.0*	22
Example 903	1886	C20 H23 N5 O5	414	8.7*	40
Example 904	1887	C21 H23 N5 O6	442	7.8*	34
Example 905	1888	C23 H27 N5 O4	438	5.6*	25
Example 906	1889	C21 H25 N5 O4 S	444	13.2*	58
Example 907	1890	C22 H27 N5 O4	426	11.3*	51
Example 908	1891	C22 H25 N5 O5	440	7.4*	33
Example 909	1892	C22 H27 N5 O4	426	5.5*	25
Example 910	1893	C23 H29 N5 O4	440	5.7*	25
Example 911	1894	C23 H29 N5 O4	440	9.4*	41
Example 912	1895	C24 H31 N5 O4	455	8.5*	37

*Yield of TFA salt.

Reference Example 7: Preparation of 2-Carbamoyl-1-(4-

chlorobenzyl)pyrrolidine.

A solution of *dl*-prolinamide hydrochloride (2.5 g, 21.8 mmol) in CH_3CN (35 mL) was treated with Et_3N (7.45 mL) and 4-chlorobenzyl chloride (3.88 g, 24.1 mmol). The reaction mixture was stirred at 70 °C for 4 h and then at 25 °C for 16 h. The resulting mixture was diluted with CH_2Cl_2 (20 mL) and was washed with water(3 x 30 mL). The organic phase was dried ($MgSO_4$) and concentrated. Chromatography (SiO_2, 1% CH_3OH-CH_2Cl_2) afforded 2-carbamoyl-1-(4-chlorobenzyl)pyrrolidine (5.21 g, 81%).

Reference Example 8: Preparation of 2-(Aminomethyl)-1-(4-chlorobenzyl)pyrrolidine.

2-carbamoyl-1-(4-chlorobenzyl)pyrrolidine was dissolved in 1M BH_3-THF (9.4 mL) and heated to 70 °C. After 16 h and 25 h, additional 0.5 equiv. of 1M BH_3-THF were added. After 40 h, 1 N aqueous HCl solution (14 mL) was added and the reaction was heated to reflux for 3 h, 3 N aqueous HCl solution (6 mL) was added and the reaction was heated for an additional 3 h. The reaction mixture was cooled to 25 °C, basicified with 4 N aqueous NaOH solution and extracted with CH_2Cl_2 (4 x 15 mL). Chromatography (SiO_2, 8:1:1 ^{i}PrOH-H_2O-NH_4OH) afforded 2-(aminomethyl)-1-(4-chlorobenzyl)pyrrolidine (1.21 g, 86%).

Optically active (*S*)-2-(aminomethyl)-1-(4-chlorobenzyl)pyrrolidine and (*R*)-2-(aminomethyl)-1-(4-chlorobenzyl)pyrrolidine were also prepared pursuant to the above method using the corresponding reactant respectively.

(*S*)-2-(aminomethyl)-1-(4-chlorobenzyl)pyrrolidine: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.40-1.80 (m, 5 H), 1.80-1.95 (m, 1 H), 2.12-2.21 (m, 1 H), 2.48-2.65 (m, 1 H), 2.66-2.78 (m, 2 H), 2.85-2.95 (m, 1 H), 3.26 (d, J = 13.2 Hz, 1 H), 3.93 (d, J = 13.2 Hz, 1 H), 7.20-7.40 (m, 4 H).

(*R*)-2-(aminomethyl)-1-(4-chlorobenzyl)pyrrolidine showed the same ^{1}H NMR with that of (*S*)-isomer.

Example 913: Preparation of 2-{(*N*-benzoylleucyl)aminomethyl}-1-(4-chlorobenzyl)pyrrolidine (Compound No. 344).

A solution of 2-(aminomethyl)-1-(4-chlorobenzyl)pyrrolidine (22.5 mg, 0.10 mmol) and *dl*-benzoylleucine (0.12 mmol) in $CHCl_3$ (1 mL) was treated with EDCI (23 mg), HOBt (16.2 mg) and Et_3N (15.2 μL), and stirred at 25 °C for 16 h. The reaction mixture was diluted with CH_2Cl_2 (0.5 mL), washed with 2 N aqueous NaOH solution (2 x 0.75 mL), dried by filtration through a PTFE membrane and concentrated to afford 2-{(*N*-benzoylleucyl)aminomethyl}-1-(4-

chlorobenzyl)pyrrolidine (compound No. **344**) (74 mg, quant) : The purity was determined by RPLC/MS (85%); ESI/MS m/e 442 (M^++H, $C_{25}H_{32}ClN_3O_2$).

Examples 914-935.

The compounds of this invention were synthesized pursuant to methods of Example 913 using the corresponding reactant respectively. Chromatography, if needed, (HPLC-C_{18}, $CH_3CN/H_2O/TFA$) afforded the desired material as the TFA salt. The ESI/MS data and yields are summarized in Table 19 and compound No. **339** and **340** showed the following ^1H NMR spectra respectively.

Table 19

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 914	330	C21 H24 Cl N3 O2	386	75*	quant
Example 915	331	C22 H26 Cl N3 O2	400	44*	70
Example 916	332	C24 H30 Cl N3 O5	476	57	quant
Example 917	333	C20 H23 Cl N4 O2	387	40	quant
Example 918	334	C22 H26 Cl N3 O2	400	68	quant
Example 919	335	C21 H23 Cl N4 O4	431	73	quant
Example 920	336	C22 H23 Cl F3 N3 O2	454	75	quant
Example 921	337	C22 H26 Cl N3 O2	400	68	quant
Example 922	338	C22 H26 Cl N3 O2	400	70	quant
Example 923	341	C22 H26 Cl N3 O2	400	80*	quant
Example 924	342	C22 H26 Cl N3 O2	400	68	quant
Example 925	343	C24 H30 Cl N3 O2	428	63	quant
Example 926	345	C23 H27 Cl N2 O2	399	68*	quant
Example 927	346	C23 H26 Cl F N2 O3	433	51	quant
Example 928	347	C24 H29 Cl N2 O2	413	47	quant
Example 929	348	C23 H27 Cl N2 O2	399	26	quant
Example 930	349	C21 H25 Cl N2 O3 S	421	42	quant
Example 931	350	C26 H33 Cl N2 O3	457	12.4	54
Example 932	351	C22 H26 Cl N3 O3	416	34	81
Example 933	352	C22 H25 Cl2 N3 O3	450	51	quant

*Yield of TFA salt.

Example 934. Compound No. **339**: 82%; ^1H NMR ($CDCl_3$) δ 1.52–1.75 (m, 4 H), 1.84–1.95 (m, 1 H), 2.10–2.20 (m, 1 H), 2.67–2.78 (m, 1 H), 2.80–2.90 (m, 1 H), 3.10–3.20 (m, 1 H), 3.25 (d, J = 13.1 Hz, 1 H), 3.50–3.60 (m, 1 H), 3.89 (d,

J = 13.1 Hz, 1 H), 4.28—4.20 (m, 2 H), 7.00—7.05 (m, 1 H), 7.12—7.29 (m, 4 H), 7.51 (t, J = 7.8 Hz, 1 H), 7.74 (d, J = 7.8 Hz, 1 H), 7.99 (d, J = 7.8 Hz, 1 H), 8.10—8.27 (m, 2 H).

Example 935. Compound No. **340:** 68%; ^{1}H NMR ($CDCl_3$) δ 1.55—1.73(m, 4 H), 1.86—1.97 (m, 1 H), 2.12—2.21 (m, 1 H), 2.67—2.76 (m, 1 H), 2.86—2.93 (m, 1 H), 3.14—3.21 (m, 1 H), 3.27 (d, J = 13.1 Hz, 1 H), 3.52—3.59 (m, 1 H), 3.89 (d, J = 13.1 Hz, 1 H), 4.09—4.21 (m, 2 H), 7.00—7.07 (m, 1 H), 7.12—7.30 (m, 4 H), 7.50 (t, J = 7.8 Hz, 1 H), 7.73 (d, J = 7.8 Hz, 1 H), 8.01 (d, J = 7.8 Hz, 1 H), 8.10—8.25 (m, 2 H).

Reference Example 9: Preparation of 3-(Aminomethyl)-1-(4-chlorobenzyl)pyrrolidine.

To a mixture of 4-carboxy-1-(4-chlorobenzyl)pyrrolidin-2-one (5.05 g, 20 mmol), EDCI (2.85 g, 22 mmol), HOBt (2.97 g, 22 mmol) and dichloromethane (100 mL) was added 0.5 M ammonia in dioxane (60 mL, 30 mmol). The reaction mixture was stirred at room temperature for 15 h and washed with 2N HCl (3 times) and 2 N NaOH aqueous solution (100 mL x 4). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated to afford 3-carbamoyl-1-(4-chlorobenzyl)pyrrolidin-2-one (1.49 g) as a colorless solid.

To a solution of 3-carbamoyl-1-(4-chlorobenzyl)pyrrolidin-2-one (1.45 g) in THF (15 mL) was added 1.0 N BH_3 in THF (25 mL). The reaction mixture was stirred at 65 °C for 15 h. After cooling to room temperature, the solvent was removed under reduced pressure. Water (30 mL) and conc. HCl (10 mL) were added and the mixture was stirred at 100 °C for 2 h and room temperature for 1 h. 2 N NaOH aqueous solution (100 mL) was added and the mixture was extracted with AcOEt (50 mL x 3). The combined organic layers were dried over K_2CO_3, filtered and concentrated. Column chromatography (SiO_2, 15% CH_3OH-5% Et_3N in CH_2Cl_2) afforded 3-(aminomethyl)-1-(4-chlorobenzyl)pyrrolidine (860 mg, 19%) as a colorless oil.

Reference Example 10: Preparation of 1-(4-Chlorobenzyl)-3-{(glycylamino)methyl}pyrrolidine.

A mixture of 3-(aminomethyl)-1-(4-chlorobenzyl)pyrrolidine (860 mg, 3.8 mmol), Et_3N (5.7 mmol), *N-tert*-butoxycarbonylglycine (704 mg), EDCI (594 mg), HOBt (673 mg), and dichloromethane (20 mL) was stirred at room temperature for 15 h. Dichloromethane (50 mL) was added and the solution was washed with 2 N NaOH solution (50 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated to afford 3-[{*N*-(*tert*-butoxycarbonyl)glycyl}aminomethyl]-1-(4-

chlorobenzyl)pyrrolidine (1.31 g, 90%).

To a solution of 3-[{*N*-(*tert*-butoxycarbonyl)glycyl}aminomethyl]-1-(4-chlorobenzyl)pyrrolidine (804 mg, 2.11 mmol) in methanol (10 mL) was added 4 N HCl in dioxane (5 mL). The solution was stirred at room temperature for 3.5 h. The reaction mixture was concentrated and 1 N NaOH solution (20 mL) was added. The mixture was extracted with dichloromethane (20 mL x 3), and the combined extracts were dried over sodium sulfate and concentrated to give desired 1-(4-chlorobenzyl)-3-{(glycylamino)methyl}pyrrolidine (599 mg, 100%): The purity was determined by RPLC/MS (100%); ESI/MS m/e 282.2 (M^{+}+H, $C_{14}H_{20}ClN_3O$).

Example 936: Preparation of 3-[{*N*-(3-Trifluoromethylbenzoyl)glycyl}aminomethyl]-1-(4-chlorobenzyl)pyrrolidine (Compound No. 1463).

A solution of 3-(trifluoromethyl)benzoyl chloride (0.058 mmol) in dichloromethane (0.2 mL) was added to a mixture of 1-(4-chlorobenzyl)-3-{(glycylamino)methyl}pyrrolidine (0.050 mmol) and piperidinomethylpolystyrene (60 mg) in chloroform (0.2 mL) and dichloromethane (1 mL). After the reaction mixture was stirred at room temperature for 2.5 h, methanol (0.30 mL) was added and the mixture was stirred at room temperature for 1 h. The reaction mixture was loaded onto Varian™ SCX column, and washed with CH_3OH (15 mL). Product was eluted off using 2 N NH_3 in CH_3OH (5 mL) and concentrated to afford (3-[{*N*-(3-trifluoromethylbenzoyl)glycyl}aminomethyl]-1-(4-chlorobenzyl)pyrrolidine (Compound No. **1463**) (22.4 mg, 99%): The purity was determined by RPLC/MS (97%); ESI/MS m/e 454.2 (M^{+}+H, $C_{22}H_{23}ClF_3N_3O_2$).

Examples 937-944.

The compounds of this invention were synthesized pursuant to methods of Example 936 using the corresponding reactant respectively. The ESI/MS data and yields are summarized in Table 20.

Table 20

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 937	1464	C22 H23 Cl F3 N3 O3	470.0	21.0	89
Example 938	1465	C23 H22 Cl F6 N3 O2	522.0	24.5	94
Example 939	1466	C21 H23 Br Cl N3 O2	466.0	20.8	90
Example 940	1467	C21 H23 Cl2 N3 O2	420.0	19.6	93

Example 941	1468	C21 H23 Cl N4 O4	431.2	19.5	91
Example 942	1469	C22 H22 Cl F4 N3 O2	472:0	21.8	92
Example 943	1470	C21 H22 Cl3 N3 O2	456.0	22.1	97
Example 944	1471	C21 H22 Cl F2 N3 O2	422.0	20.9	99

Example 945: Preparation of 3-[{*N*-(2-Amino-4,5-difluorobenzoyl)glycyl}aminomethyl]-1-(4-chlorobenzyl)pyrrolidine (Compound No. 1506).

A solution of 1-(4-chlorobenzyl)-3-{(glycylamino)methyl}pyrrolidine (0.050 mmol) in $CHCl_3$ (1.35 mL) and *tert*-butanol (0.05 mL) was treated with 2-amino-4,5-difluorobenzoic acid (0.060 mmol), diisopropylcarbodiimide (0.060 mmol), and HOBt (0.060 mmol). The reaction mixture was stirred at room temperature for 19 h. The mixture was loaded onto Varian™ SCX column, and washed with $CH_3OH/CHCl_3$ 1:1 (10 mL) and CH_3OH (10 mL). Product was eluted off using 2 N NH_3 in CH_3OH (5 mL) and concentrated to afford 3-[{*N*-(2-amino-4,5-difluorobenzoyl)glycyl}aminomethyl]-1-(4-chlorobenzyl)pyrrolidine (Compound No. **1506**) (22.0 mg, quant): The purity was determined by RPLC/MS (92%); ESI/MS m/e 437 ($C_{21}H_{23}ClF_2N_4O_2$).

Examples 946-952.

The compounds of this invention were synthesized pursuant to methods of Example 945 using the corresponding reactant respectively. The ESI/MS data and yields are summarized in Table 21.

Table 21

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 946	1506	C21 24 Br Cl N4 O2	481	20.6	86
Example 947	1507	C21 H24 F Cl N4 O2	419	21.7	quant
Example 948	1509	C27 H28 Cl N3 O2	462	26.5	quant
Example 949	1510	C21 H24 Cl I N4 O2	527	22.0	84
Example 950	1511	C19 H21 Br Cl N3 O2 S	472	23.7	quant
Example 951	1512	C21 H24 Cl2 N4 O2	435	22.3	quant
Example 952	1513	C27 H28 Cl N3 O4 S	526	24.6	94

Reference Example 11: Preparation of 1-(4-Chlorobenzyl)nipecotic acid.

4-Chlorobenzyl chloride (6.42 g, 39.9 mmol) and $^iPr_2NEt$ (7.74 g, 40.0 mmol)

were added to a solution of ethyl nipecotate (6.29 g, 40.0 mmol) in CH_3CN (15 mL). The reaction mixture was stirred at 70 °C for 1.5 h. The solvent was removed under reduced pressure. Saturated aqueous $NaHCO_3$ (50 mL) was added to the residue and the mixture was extracted with EtOAc (100 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford ethyl 1-(4-chlorobenzyl)nipecotate as a red yellow oil (11.025 g, 97.8%) used without further purification. The purity was determined by RPLC/MS (97%); ESI/MS m/e 382.2 (M^++H, $C_{15}H_{21}ClNO_2$).

A solution of LiOH (1.66 g) in H_2O (25 mL) was added to the solution of ethyl 1-(4-chlorobenzyl)nipecotate in THF (60 mL) and CH_3OH (20 mL). The reaction mixture was stirred at room temperature for 15 h. The solvent was removed under reduced pressure to afford an amorphous solid which was purified by column chromatography (SiO_2, 50% CH_3OH-CH_2Cl_2) to yield 1-(4-chlorobenzyl)nipecotic acid (9.75 g, 98.2%) as a pale yellow amorphous solid. The purity was determined by RPLC/MS (>95%); ESI/MS m/e 254.0 (M^++H, $C_{13}H_{17}ClNO_2$).

Reference Example 12: Preparation of 1-(4-Chlorobenzyl)-3-{(*tert*-butoxycarbonyl)amino}piperidine.

A solution of 1-(4-chlorobenzyl)nipecotic acid (7.06 g, 27.8 mmol) in ^{t}BuOH (500 mL) was treated with Et_3N (3.38 g) and activated 3 Å molecular sieves (30 g). Diphenylphosphoryl azide (8.58 g) was added, and the reaction mixture was warmed at reflux for 18 h. The mixture was cooled and the solvent was reflux for 18 h. The mixture was cooled and the solvent was remove under vacuum. The residue was dissolved in EtOAc (500 mL), and the organic phase was washed with saturated aqueous $NaHCO_3$ (2 x 100 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo. Chromatography (SiO_2, 25% EtOAc-hexane) afforded 1-(4-chlorobenzyl)-3-{(*tert*-butoxycarbonyl)amino}piperidine (2.95 g, 32.6%) as a white crystalline solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.4-1.75 (br, 4 H), 2.2-2.7 (br, 4 H), 3.5 (br, 2 H), 3.8 (br, 1 H), 7.3 (br, 4 H); The purity was determined by RPLC/MS (>99%); ESI/MS m/e 269.2 (M^++H-56, $C_{17}H_{26}ClN_2O_2$).

Reference Example 13: Preparation of 3-Amino-1-(4-chlorobenzyl)piperidine.

A solution of 1-(4-chlorobenzyl)-3-{(*tert*-butoxycarbonyl)amino}piperidine (2.55 g, 7.85 mmol) in CH_3OH (25 mL) was treated with 1 N HCl-Et_2O (50 mL). The reaction mixture was stirred at 25 °C for 15 h. The solvent was removed under reduced pressure to afford 3-amino-1-(4-chlorobenzyl)piperidine dihydrochloride as an amorphous solid (2.49 g, quant).

The purity was determined by RPLC/MS (>95%),; ESI/MS m/e 225.2 (M^{+}+H, $C_{12}H_{18}ClN_2$).

Example 953: Preparation of 1-(4-Chlorobenzyl)-3-[{*N*-(3-methylbenzoyl)glycyl}amino]piperidine (Compound No. 355).

N-(3-Methylbenzoyl)glycine (10.6 mg, 0.055 mmol), EDCI (10.5 mg) and 1-hydroxybenzotriazole hydrate (7.4 mg) were added to a solution of 1-(4-chlorobenzyl)-3-aminopiperidine dihydrochloride (14.9 mg, 0.050 mmol) and Et_3N (15.2 mg) in $CHCl_3$ (2.5 mL). The reaction mixture was stirred at 25 °C for 16 h, washed with 2 N aqueous NaOH (2 mL x 2) and brine (1 mL). After filtration through PTFE membrane filter, the solvent was removed under reduced pressure to afford 1-(4-chlorobenzyl)-3-[{*N*-(3-methylbenzoyl)glycyl}amino]piperidine (compound No. **355**) as a pale yellow oil (17.4 mg, 87%): The purity was determined by RPLC/MS (97%); ESI/MS m/e 400.0 (M^{+}+H, $C_{22}H_{26}ClN_3O_2$).

Examples 954-982.

The compounds of this invention were synthesized pursuant to methods of Example 953 using the corresponding reactant respectively. The ESI/MS data and yields are summarized in Table 22 and compound No. **358** showed the following ^{1}H NMR spectra.

Table 22

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 954	354	C21 H24 Cl N3 O2	386	16.1	83
Example 955	356	C20 H23 Cl N4 O2	387	19.4	100
Example 956	357	C22 H26 Cl N3 O2	400	16.8	84
Example 957	359	C22 H26 Cl N3 O2	400	8.9	17
Example 958	360	C22 H25 Cl N4 O4	445	25.6	quant
Example 959	361	C23 H27 Cl N2 O2	399	15.5	29
Example 960	362	C24 H29 Cl N2 O3	429	12.4	58
Example 961	363	C21 H25 Cl N2 O2 S	405	22.2	quant
Example 962	364	C24 H29 Cl N2 O4	445	20.7	93
Example 963	365	C24 H29 Cl N2 O2	413	15.6	75
Example 964	366	C23 H26 Cl F N2 O3	433	21.6	100
Example 965	367	C23 H27 Cl N2 O2	399	11.9	60
Example 966	368	C22 H25 Cl N2 O2	385	16.0	83
Example 967	369	C22 H24 Cl2 N2 O2	419	13.9	60
Example 968	370	C26 H33 Cl N2 O3	457	15.9	54

Example 969	371	C25 H31 Cl N2 O3	443	19.6	84
Example 970	372	C21 H25 Cl N2 O3 S	421	23.0	quant
Example 971	373	C23 H28 Cl N3 O2	414	19.1	92
Example 972	374	C24 H30 Cl N3 O3	444	18.6	84
Example 973	375	C23 H27 Cl2 N3 O2	448	18.0	80
Example 974	376	C24 H30 Cl N3 O3	444	19.6	88
Example 975	377	C25 H31 Cl2 N3 O2	476	20.7	87
Example 976	378	C27 H33 Cl F N3 O2	486	23.9	98
Example 977	379	C25 H30 Cl N3 O3	456	33.3	quant
Example 978	380	C24 H30 Cl N3 O2	428	9.8	46
Example 979	381	C21 H26 Cl N3 O3 S	436	10.3	47
Example 980	382	C22 H26 Cl N3 O3	416	24.4	quant
Example 981	383	C22 H25 Cl2 N3 O3	450	27.5	quant

Example 982. Compound No. **358:** 88%; ^{1}H NMR ($CDCl_3$) δ 1.53—1.75 (m, 4 H), 2.12—2.20 (m, 1 H), 2.37—2.50 (m, 2 H), 2.53—2.61 (m, 1 H), 3.38—3.50 (m, 2 H), 2.53—2.61 (m, 1 H), 3.38—3.50 (m, 2 H), 4.06—4.20 (m, 3 H), 7.10—7.13 (m, 1 H), 7.18—7.30 (m, 4 H), 7.59 (t, J = 7.8 Hz, 1 H), 7.79 (d, J = 7.8 Hz, 1 H), 8.01 (d, J = 7.8 Hz, 1 H), 8.11 (s, 1 H).

Reference Example 14: Preparation of 1-benzyl-4-[{*N*-(*tert*-butoxycarbonyl)glycyl}amino]piperidine.

A solution of 4-amino-1-benzylpiperidine (3.80 g, 20 mmol) in CH_2Cl_2 (40 mL) was treated with *N*-(*tert*-butoxycarbonyl)glycine (3.48 g, 20 mmol), EDCI (4.02 g, 21 mmol) and HOBt (2.83 g, 21 mmol). After the reaction mixture was stirred at room temperature for 12 h, 2 N NaOH solution (20 mL) was added. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (20 mL x 2). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography (SiO_2, ethyl acetate/MeOH/Et_3N = 85/12/3) afforded 1-benzyl-4-{N-(*tert*-butoxycarbonyl)glycyl}aminopiperidine (6.59 g, 95%).

Reference Example 15: Preparation of 1-(4-Chlorobenzyl)-4-(glycylamino)piperidine.

To a solution of 1-benzyl-4-{N-(*tert*-butoxycarbonyl)glycyl}aminopiperidine (6.59 g) in methanol (80 mL) was added 4 N HCl in dioxane (19 mL). The solution was stirred at room temperature for 2 h. The reaction mixture was concentrated and 2 N aqueous NaOH solution (20

mL) was added. The mixture was extracted with dichloromethane (40 mL x 3), and the combined extracts were dried over anhydrous sodium sulfate and concentrated. Column chromatography (SiO_2, AcOEt/MeOH/Et_3N = 85/12/3) gave 1-(4-chlorobenzyl)-4-(glycylamino)piperidine (3.91 g, 83%): ^{1}H NMR ($CDCl_3$, 400 MHz) *d* 1.47-1.59 (m, 2 H), 1.59 (br, 2 H), 1.76-1.96 (m, 2 H), 2.10-2.19 (m, 2 H), 2.75-2.87 (m, 2 H), 3.29 (s, 2 H), 3.50 (s, 2 H), 3.65-3.89 (m, 1 H), 7.15-7.23 (m, 1 H), 7.23-7.33 (m, 5 H).

Other 4-acylamino-1-benzylpiperidines were also synthesized pursuant to methods of Reference Example 13 and 14 using the corresponding reactant respectively.

4-(β-alanylamino)-1-benzylpiperidine: 2.46 g, 51% (2 steps).

1-benzyl-4-((*S*)-leucylamino)piperidine: 1.78 g, 74% (2 steps).

1-benzyl-4-((*R*)-leucylamino)piperidine: 1.48 g, 61% (2 steps).

Example 983: Preparation of 4-(*N*-benzoylglycyl)amino-1-benzylpiperidine (Compound No. 386).

A solution of benzoyl chloride (0.060 mmol) in chloroform (0.4 mL) was added to a solution of 1-(4-chlorobenzyl)-4-(glycylamino)piperidine (0.050 mmol) and triethylamine (0.070 mmol) in chloroform (1.0 mL). After the reaction mixture was agitated at room temperature for 2.5 h, (aminomethyl)polystyrene resin (1.04 mmol/g, 50 mg, 50 mmol) was added and the mixture was agitated at room temperature for 12 h. The reaction mixture was filtered and the resin was washed with dichloromethane (0.5 mL). The filtrate and washing were combined, dichloromethane (4 mL) was added, and the solution was washed with 2 N aqueous NaOH solution (0.5 mL) to give 4-(*N*-benzoylglycyl)amino-1-benzylpiperidine (compound No. **386**) (11.3 mg, 64%): The purity was determined by RPLC/MS (94 %); ESI/MS m/e 352.0 (M^++H, $C_{21}H_{25}N_3O_2$).

Examples 984-1034.

The compounds of this invention were synthesized pursuant to methods of Example 983 using the corresponding reactant respectively. The ESI/MS data and yields are summarized in Table 23.

Table 23

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 984	384	C22 H26 Cl N3 O2	400	60.0	quant
Example 985	385	C21 H23 Cl N4 O4	431	58.7	91
Example 986	387	C25 H27 N3 O2	402.5	15.5	77
Example 987	388	C21 H24 N4 O4	397.0	16.2	82
Example 988	389	C23 H27 N3 O4	410.0	16.2	79
Example 989	390	C22 H24 F3 N3 O2	420.0	17.4	83
Example 990	391	C22 H23 F4 N3 O2	438.0	18.4	84
Example 991	392	C22 H24 F3 N3 O3	436.0	17.1	79
Example 992	393	C21 H24 Br N3 O2	430.0	18.0	84
Example 993	394	C21 H24 Cl N3 O2	386.0	16.4	85
Example 994	395	C21 H24 Br N3 O2	430.0	17.2	80
Example 995	396	C21 H23 F2 N3 O2	388.0	15.1	78
Example 996	397	C21 H23 Cl2 N3 O2	420.0	11.7	56
Example 997	398	C22 H27 N3 O2	366.0	13.1	72
Example 998	399	C26 H29 N3 O2	416.0	15.8	76
Example 999	400	C22 H26 N4 O4	411.0	17.4	85
Example 1000	401	C24 H29 N3 O4	424.0	16.9	80
Example 1001	402	C23 H26 F3 N3 O2	434.0	17.7	82
Example 1002	403	C23 H25 F4 N3 O2	452.0	18.6	82
Example 1003	404	C23 H26 F3 N3 O3	450.0	17.8	79
Example 1004	405	C22 H26 Br N3 O2	444.0	17.9	81
Example 1005	406	C22 H26 Cl N3 O2	400.0	15.5	78
Example 1006	407	C22 H26 Br N3 O2	444.0	17.8	80
Example 1007	408	C22 H25 F2 N3 O2	402.0	15.6	78
Example 1008	409	C22 H25 Cl2 N3 O2	434.0	17.6	81
Example 1009	410	C25 H33 N3 O2	408.0	16.2	79
Example 1010	411	C29 H35 N3 O2	458.5	18.8	82
Example 1011	412	C25 H32 N4 O4	453.0	19.4	86
Example 1012	413	C27 H35 N3 O4	466.0	19.8	85
Example 1013	414	C26 H32 F3 N3 O2	476.0	20.2	85
Example 1014	415	C26 H31 F4 N3 O2	494.0	20.5	83
Example 1015	416	C26 H32 F3 N3 O3	492.0	19.5	79
Example 1016	417	C25 H32 Br N3 O2	486.0	19.1	79
Example 1017	418	C25 H32 Cl N3 O2	442.0	17.7	80
Example 1018	419	C25 H32 Br N3 O2	486.0	20.3	83
Example 1019	420	C25 H31 F2 N3 O2	444.0	18.6	84
Example 1020	421	C25 H31 Cl2 N3 O2	476.0	19.4	81
Example 1021	422	C25 H33 N3 O2	408.0	14.4	71

Example 1022	423	C29 H35 N3 O2	458.0	16.4	72
Example 1023	424	C25 H32 N4 O4	453.0	18.1	80
Example 1024	425	C27 H35 N3 O4	466.0	16.4	70
Example 1025	426	C26 H32 F3 N3 O2	476.0	17.3	73
Example 1026	427	C26 H31 F4 N3 O2	494.0	18.8	76
Example 1027	428	C26 H32 F3 N3 O3	492.0	18.4	75
Example 1028	429	C25 H32 Br N3 O2	486.0	17.9	74
Example 1029	430	C25 H32 Cl N3 O2	442.0	15.7	71
Example 1030	431	C25 H32 Br N3 O2	486.0	17.7	73
Example 1031	432	C25 H31 F2 N3 O2	444.0	16.6	75
Example 1032	433	C25 H31 Cl2 N3 O2	476.0	18.7	78
Example 1033	1016	C22 H23 Cl F3 N3 O2	454	32.5*	53
Example 1034	1017	C21 H24 Cl N3 O2	386	55.2*	quant

*Yield of TFA salt.

Reference Example 16: Preparation of 3-Carbamoyl-1-(4-chlorobenzyl)piperidine.

A solution of nipecotamide (6.40 g, 50 mmol) in CH_3CN (150 mL) and ethanol (20 mL) was treated with Et_3N (7.0 mL, 50 mmol) and 4-chlorobenzyl chloride (8.05 g, 50 mmol). The reaction mixture was stirred at 50 °C for 16 h. After cooling to room temperature, saturated aqueous $NaHCO_3$ (50 mL) and water (150 mL) was added to the reaction mixture. The mixture was extracted with ethyl acetate (150 mL x 3) and the combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to give a pale red solid. The crude solid was washed with ether (100 mL) to afford 3-carbamoyl-1-(4-chlorobenzyl)piperidine (6.98 g, 54%).

Reference Example 17: Preparation of 3-(Aminomethyl)-1-(4-chlorobenzyl)piperidine.

3-Carbamoyl-1-(4-chlorobenzyl)piperidine (3.80 g, 15 mmol) was dissolved in THF (30 mL) and 1 M BH_3-THF (9.4 mL) was added to the solution. The reaction mixture was stirred at 70 °C for 15 h. After the mixture was cooled to 0 °C, 2 N aqueous HCl solution (50 mL) was added and the mixture was stirred at room temperature for additional 3 h , basicified with 4 N aqueous NaOH solution, and extracted with ethyl acetate (100 mL x 3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. Column chromatography (SiO_2, ethyl acetate/EtOH/Et_3N = 80/15/5) afforded 3-(aminomethyl)-1-(4-chlorobenzyl)piperidine (2.05 g, 55%): ^1H NMR ($CDCl_3$, 400 MHz) δ 1.00-1.09 (m, 1 H), 1.50-1.87 (m, 7 H), 1.97-2.06 (m, 1 H), 2.65-2.77

(m, 2 H), 3.16-3.26 (m, 2 H), 3.32 (s, 2 H), 3.40 (d, J = 13.3 Hz, 1 H), 3.49 (d, J = 13.3 Hz, 1 H), 7.22-7.33 (m, 5 H).

Example 1035: Preparation of 3-{(*N*-Benzoylglycyl)amino}methyl-1-(4-chlorobenzyl)piperidine (Compound No. 434).

A solution of benzoyl chloride (0.060 mmol) in chloroform (0.4 mL) was added to a solution of 3-(aminomethyl)-1-(4-chlorobenzyl)piperidine (0.050 mmol) and triethylamine (0.070 mmol) in chloroform (1.0 mL). After the reaction mixture was agitated at room temperature for 2.5 h, (aminomethyl)polystyrene resin (1.04 mmol/g, 50 mg, 50 mmol) was added and the mixture was agitated at room temperature for 12 h. The reaction mixture was filtered and the resin was washed with dichloromethane (0.5 mL). The filtrate and washing were combined, dichloromethane (4 mL) was added, and the solution was washed with 2 N aqueous NaOH solution (0.5 mL) to give 3-{(*N*-benzoylglycyl)amino}methyl-1-(4-chlorobenzyl)piperidine (compound No. **434**) (14.7 mg, 74%): The purity was determined by RPLC/MS (91%); ESI/MS m/e 400 (M^{+}+H, $C_{22}H_{26}ClN_3O_2$).

Examples 1036-1058.

The compounds of this invention were synthesized pursuant to methods of Example 1035 using the corresponding reactant respectively. The ESI/MS data and yields are summarized in Table 24.

Table 24

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 1036	435	C26 H28 Cl N3 O2	450	16.0	71
Example 1037	436	C22 H25 Cl N4 O4	445	18.9	85
Example 1038	437	C24 H28 Cl N3 O4	458	18.2	79
Example 1039	438	C23 H25 Cl F3 N3 O2	468	19.0	81
Example 1040	439	C23 H24 Cl F4 N3 O2	486	20.2	83
Example 1041	440	C23 H25 Cl F3 N3 O3	484	18.9	78
Example 1042	441	C22 H25 Br Cl N3 O2	478	19.2	80
Example 1043	442	C22 H25 Cl2 N3 O2	434	17.3	80
Example 1044	443	C22 H25 Br Cl N3 O2	478	18.8	79
Example 1045	444	C22 H24 Cl F2 N3 O2	436	16.7	77
Example 1046	445	C22 H24 Cl3 N3 O2	468	17.9	76
Example 1047	446	C23 H28 Cl N3 O2	414	14.6	71
Example 1048	447	C27 H30 Cl N3 O2	464	17.0	73

Example 1049	448	C23 H27 Cl N4 O4	459	19.5	85
Example 1050	449	C25 H30 Cl N3 O4	472	17.1	72
Example 1051	450	C24 H27 Cl F3 N3 O2	482	19.4	81
Example 1052	451	C24 H26 Cl F4 N3 O2	500	18.2	73
Example 1053	452	C24 H27 Cl F3 N3 O3	498	18.8	76
Example 1054	453	C23 H27 Br Cl N3 O2	492	19.4	79
Example 1055	454	C23 H27 Cl2 N3 O2	448	16.5	74
Example 1056	455	C23 H27 Br Cl N3 O2	492	19.3	78
Example 1057	456	C23 H26 Cl F2 N3 O2	450	17.1	76
Example 1058	457	C23 H26 Cl3 N3 O2	482	16.9	70

Reference Example 18: Preparation of 4-(Aminomethyl)-1-(4-chlorobenzyl)piperidine.

A solution of 4-(aminomethyl)piperidine (7.00 g, 61.3 mmol) in CH_3CN (100 mL) was treated sequentially with K_2CO_3 (3.02 g) and 4-chlorobenzyl chloride (3.52 g, 21.8 mmol). The reaction mixture was heated to 60 °C for 16 h, cooled to 25 °C and concentrated. The residue was partitioned between CH_2Cl_2 (75 mL) and water (50 mL), and was washed with water (2 x 50 mL) and brine (1 x 50 mL). The organic phase was dried ($MgSO_4$) and concentrated. Chromatography (SiO_2, 4% H_2O-^{i}PrOH) afforded 4-(aminomethyl)-1-(4-chlorobenzyl)piperidine (3.58 g, 69%).

Example 1059: Preparation of 4-{(*N*-Benzoylglycyl)amino}methyl-1-(4-chlorobenzyl)piperidine (Compound No. 458).

A solution of 4-(aminomethyl)-1-(4-chlorobenzyl)piperidine (50 mg, 0.21 mmol) in CH_2Cl_2 (1 mL) was treated with hippuric acid (38 mg, 0.21 mmol), EDCI (48 mg, 0.24 mmol), HOBt (31 mg, 0.23 mmol) and Et_3N (38 µL, 0.27 mmol). The reaction mixture was stirred for 16 h at 25 °C, diluted with 1 mL of CH_2Cl_2, washed with 2 N aqueous NaOH solution (2 x 0.75 mL), dried ($MgSO_4$) and concentrated. Chromatography (SiO_2, 6 to 8% CH_3OH/CH_2Cl_2 gradient elution) afforded 4-{(*N*-benzoylglycyl)amino}methyl-1-(4-chlorobenzyl)piperidine (compound No. **458**) which was treated with TFA to give a TFA salt(105 mg, 97%): The purity was determined by RPLC/MS (85%); ESI/MS m/e 400 (M^++H, $C_{22}H_{26}ClN_3O_2$).

Examples 1060-1086.

The compounds of this invention were synthesized pursuant to methods of Example 1059 using the corresponding reactant respectively. The ESI/MS data and yields are summarized in Table 25.

Table 25

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 1060	459	C23 H28 Cl N3 O2	414	86*	78
Example 1061	460	C23 H28 Cl N3 O2	414	55	quant
Example 1062	461	C23 H25 Cl F3 N3 O2	468	65	quant
Example 1063	462	C23 H28 Cl N3 O2	414	61	quant
Example 1064	463	C23 H28 Cl N3 O2	414	54	quant
Example 1065	464	C25 H32 Cl N3 O5	490	56	quant
Example 1066	465	C21 H 25 Cl N4 O2	401	38	96
Example 1067	466	C22 H25 Cl N4 O4	445	15	34
Example 1068	557	C23 H28 Cl N3 O2	414	58*	66
Example 1069	558	C23 H 28 Cl N3 O2	414	55	quant
Example 1070	618	C25 H32 Cl N3 O2	442	58	quant
Example 1071	686	C26 H34 Cl N3 O2	456	62	quant
Example 1072	749	C34 H37 Cl N4 O2	569	7.2*	18
Example 1073	750	C24 H30 Cl N3 O3	444	4.7*	14
Example 1074	840	C24 H29 Cl N2 O2	413	52*	58
Example 1075	841	C23 H27 Cl N2 O2	399	52	quant
Example 1076	842	C23 H26 Cl2 N2 O2	433	55	quant
Example 1077	843	C25 H31 Cl N2 O2	427	58	quant
Example 1078	844	C24 H29 Cl N2 O2	413	56	quant
Example 1079	845	C24 H29 Cl N2 O4 S	477	62	quant
Example 1080	846	C29 H31 Cl N2 O3	491	43	88
Example 1081	847	C24 H28 Cl F N2 O3	447	54	quant
Example 1082	848	C25 H31 Cl N2 O2	427	47	quant
Example 1083	849	C25 H31 Cl N2 O4	459	55	quant
Example 1084	850	C22 H27 Cl N2 O3 S	435	46	quant
Example 1085	873	C20 H28 Cl N3 O2	378	44.8	quant
Example 1086	874	C23 H27 Cl2 N3 O3	464	51	quant

*Yield of TFA salt.

Reference Example 19: Preparation of 1-(4-Chlorobenzyl)-4-{*N*-(3,3-diphenylpropyl)aminomethyl}piperidine.

4-(Aminomethyl)-1-(4-chlorobenzyl)piperidine (120 mg) was alkylated with 3,3-diphenylpropyl methanesulfonate (1.0 equiv.) in the presence of NaI (2.6 equiv.) in CH_3CN at 70 °C for 16 h. General workup and column chromatography (SiO_2) afforded 1-(4-chlorobenzyl)-4-{*N*-(3,3-

diphenylpropyl)aminomethyl}piperidine (118 mg, 54%): The purity was determined by RPLC (98%).

Reference Example 20: Preparation of 1-(4-Chlorobenzyl)-4-{*N*-(2,2-diphenylethyl)aminomethyl}piperidine.

Reductive amination of 4-(aminomethyl)-1-(4-chlorobenzyl)piperidine (120 mg) with 2,2-diphenylacetaldehyde (0.66 equiv.)and polymer-supported borohydride in methanol at 25 °C for 16 h, followed by general workup and column chromatography (SiO_2) afforded 1-(4-chlorobenzyl)-4-{*N*-(2,2-diphenylethyl)aminomethyl}piperidine (70 mg, 49%): The purity was determined by RPLC (98%).

Example 1087: Preparation of 4-{*N*-(*N*-Benzoylglycyl)-*N*-(2,2-diphenylethyl)aminomethyl}-1-(4-chlorobenzyl)piperidine (Compound No. 524).

A solution of 1-(4-chlorobenzyl)-4-{*N*-(2,2-diphenylethyl)aminomethyl}piperidine (0.084 mmol) in CH_2Cl_2 was treated with hippuric acid (1.1 equiv.), HBTU (1.1 equiv.), HOBt (1.1 equiv.). The reaction mixture was stirred at 40 °C for 24 h. General workup and preparative TLC (SiO_2) afforded 4-{*N*-(*N*-benzoylglycyl)-*N*-(2,2-diphenylethyl)aminomethyl}-1-(4-chlorobenzyl)piperidine (Compound No. 524) (8.5 mg, 17%): The purity was determined by RPLC/MS (98%); ESI/MS m/e 580 (M^{+}+H, $C_{36}H_{38}ClN_3O_2$).

Examples 1088-1090.

The compounds of this invention were synthesized pursuant to methods of Example 1087 using the corresponding reactant respectively. The ESI/MS data and yields are summarized in Table 26.

Table 26

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 1088	521	C38 H39 Cl F3 N3 O2	662	5.5	10
Example 1089	522	C37 H37 Cl F3 N3 O2	648	8.6	16
Example 1090	523	C37 H40 Cl N3 O2	594	4.8	10

Reference Example 21: Preparation of 1-(4-Chlorobenzyl)-4-{(valylamino)methyl}piperidine.

A solution of 4-(aminomethyl)-1-(4-chlorobenzyl)piperidine (1.0 g, 4.2

mmol) in CH_2Cl_2 (21 mL) was treated with Et_3N (0.76 mL, 5.44 mmol), *dl-N-*(*tert*-butoxycarbonyl)valine (1.09 g, 5.03 mmol), EDCI (883 mg, 4.61 mmol) and HOBt (623 mg, 4.61 mmol). The reaction mixture was stirred at 25 °C for 16 h. The resulting solution was diluted with CH_2Cl_2 (20 mL), and washed with 2 N NaOH solution (2 x 20 mL), brine (1 x 20 mL) and dried ($MgSO_4$). Concentration and chromatography (SiO_2, 3% CH_3OH/CH_2Cl_2) afforded 1-(4-chlorobenzyl)-4-[{(*N*-Boc-valyl)amino}methyl]piperidine (1.1 g, 60%) as a pale amber oil: ESI/MS m/e 438 (M^++H).

1-(4-Chlorobenzyl)-4-[{(*N*-Boc-valyl)amino}methyl]piperidine (1.1 g, 2.51 mmol) was dissolved in 3 M HCl-CH_3OH solution (25 mL) and stirred at 25 °C for 1 h. The reaction mixture was concentrated and the resulting salt was dissolved in 3:1 ^{t}BuOH-H_2O (25 mL). Anion (OH^-) exchange resin was added until the solution was slightly basic. Filtration and concentration afforded 1-(4-chlorobenzyl)-4-{(valylamino)methyl}piperidine (819 mg, 97%) which required no further purification: RPLC (97%); ESI/MS 338.1 (M^++H, $C_{18}H_{28}ClN_3O$).

Other 4-{(acylamino)methyl}-1-(4-chlorobenzyl)piperidines were also synthesized pursuant to methods of Reference Example 20 using the corresponding reactant respectively.

1-(4-chlorobenzyl)-4-{(glycylamino)methyl}piperidine: 0.830 g, 67% (2 steps); ESI/MS 269 (M^++H).

1-(4-chlorobenzyl)-4-{(serylamino)methyl}piperidine: 0.286 g, 20% (2 steps); ESI/MS 326 (M^++H).

4-{(alanylamino)methyl}-1-(4-chlorobenzyl)piperidine: 1.20 g, 65% (2 steps); ESI/MS 310 (M^++H).

1-(4-chlorobenzyl)-4-{(prolylamino)methyl}piperidine: 1.48 g, 86% (2 steps); ESI/MS 336 (M^++H).

1-(4-chlorobenzyl)-4-{(glutaminylamino)methyl}piperidine: 0.830 g, 27% (2 steps); ESI/MS 367 (M^++H).

1-(4-chlorobenzyl)-4-{((2-methylalanyl)amino)methyl}piperidine: 2.24 g, 62% (2 steps); ESI/MS 324 (M^++H).

1-(4-chlorobenzyl)-4-{((*O*-methylseryl)amino)methyl}piperidine: 0.686 g, 38% (2 steps); ESI/MS 340 (M^++H).

1-(4-chlorobenzyl)-4-{((1-aminocyclopropylcarbonyl)amino)methyl}piperidine: 2.03 g, 82% (2 steps); ESI/MS 322 (M^++H).

1-(4-chlorobenzyl)-4-{(leucylamino)methyl}piperidine: 1.30 g, 58% (2 steps); ESI/MS 352 (M^++H).

1-(4-chlorobenzyl)-4-{((*O*-benzylseryl)amino)methyl}piperidine: 1.34 g, 56% (2 steps); ESI/MS 416 (M^++H).

Reference Example 22: Preparation of 1-(*tert*-Butoxycarbonyl)-4-[{*N*-(9-fluorenylmethyloxycarbonyl)glycyl}aminomethyl]piperidine.

A solution of 4-(aminomethyl)-1-(*tert*-butoxycarbonyl)piperidine (5.72 g) in CH_2Cl_2 (150 mL) was treated with Et_3N (3.51 g), *N*-(9-fluorenylmethyloxycarbonyl)glycine (7.93 g, 26.7 mmol), EDCI (3.80 g) and HOBt (4.33 g). After the reaction mixture was stirred at room temperature for 5 h, the mixture was washed with water (100 mL x 3) and brine (100 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated. Recrystallization from CH_3CN/CH_3OH (150 mL/1 mL) at 0 °C afforded 1-(*tert*-Butoxycarbonyl)-4-[{*N*-(9-fluorenylmethyloxycarbonyl)glycyl}aminomethyl]piperidine (5.75 g, 44%) as pale yellow crystals.

Reference Example 23: Preparation of 4-[{*N*-(9-Fluorenylmethyloxycarbonyl)glycyl}aminomethyl]piperidine.

To 1-(*tert*-Butoxycarbonyl)-4-[{*N*-(9-fluorenylmethyloxycarbonyl)glycyl}aminomethyl]piperidine (3.17 g, 6.42 mmol) was added 4 N HCl in dioxane (50 mL). The solution was stirred at room temperature for 5 h. The reaction mixture was concentrated to give 4-[{*N*-(9-fluorenylmethyloxycarbonyl)glycyl}aminomethyl]piperidine (3.85 g) as a white solid. The product was used without further purification.

Reference Example 24: Preparation of 4-[{*N*-(9-Fluorenylmethyloxycarbonyl)glycyl}aminomethyl]-1-(4-methylthiobenzyl)piperidine.

To A solution of 4-[{*N*-(9-fluorenylmethyloxycarbonyl)glycyl}aminomethyl]piperidine (1.00 g, 2.33 mmol) in 1% AcOH/DMF (15 mL) were added 4-methylthiobenzaldehyde (1.24 g) and $NaBH(OAc)_3$ (2.56 g). The reaction mixture was stirred at 60 °C for 1 h, cooled to room temperature, and concentrated. Saturated aqueous $NaHCO_3$ solution (50 mL) was added and the mixture was extracted with AcOEt (50 mL x 2). The combined extracts were dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography ($SiO2$, 5%-10% CH_3OH/CH_2Cl_2) afforded 4-[{*N*-(9-fluorenylmethyloxycarbonyl)glycyl}aminomethyl]-1-(4-methylthiobenzyl)piperidine (602 mg) as a colorless oil.

Reference Example 25: Preparation of .1-(4-Ethylbenzyl)-4-[{*N*-(9-fluorenylmethyloxycarbonyl)glycyl}aminomethyl]piperidine.

To A solution of 4-[{*N*-(9-fluorenylmethyloxycarbonyl)glycyl}aminomethyl]piperidine (1.00 g, 2.33 mmol) in 2.5% AcOH/CH_3OH (80 mL) were added 4-ethylbenzaldehyde (1.09 g, 8.16 mmol) and $NaBH_3CN$ (6.59 g, 10.5 mmol). The reaction mixture was stirred at 60 °C for 13 h. After the mixture was cooled to room temperature, 1 N aqueous NaOH solution (50 mL) and dichloromethane (50 mL) were added. The organic layer was separated and the aqueous layer was extracted with dichloromethane (50 mL x 3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography (SiO2, CH_3OH/AcOEt 2 : 8) afforded 1-(4-ethylbenzyl)-4-[{*N*-(9-fluorenylmethyloxycarbonyl)glycyl}aminomethyl]piperidine (740 mg, 62%).

Reference Example 26: Preparation of 4-{(Glycylamino)methyl}-1-(4-methylthiobenzyl)piperidine.

A solution of 4-[{*N*-(9-fluorenylmethyloxycarbonyl)glycyl}aminomethyl]-1-(4-methylthiobenzyl)piperidine (590 mg) and piperidine (1 mL) in DMF (4 mL) was stirred at room temperature for 2 h. Concentration and column chromatography (SiO_2, Et_3N : CH_3OH : CH_2Cl_2 = 1 : 1 : 9) afforded 4-{(glycylamino)methyl}-1-(4-methylthiobenzyl)piperidine (365 mg) as a white solid: ^1H NMR ($CDCl_3$, 270 MHz) δ 1.25(dd, J = 12 Hz, 4.1 Hz, 2 H), 1.34(dd, J = 12 Hz, 4.1 Hz, 2 H), 1.51 (br-s, 2 H), 1.66 (d, J = 12 Hz, 2 H), 1.77 (d, J = 7.3 Hz, 1 H), 1.94 (t, J = 9.5 Hz, 2 H), 2.48 (s, 3 H), 2.80 (d, J = 12 Hz, 2 H), 3.18 (t, J = 6.2 Hz, 2 H), 3.35 (s, 2 H), 3.45 (s, 2 H), 7.18-7.29 (m, 4 H), 7.35 (br-s, 1 H).

1-(4-Ethylbenzyl)-4-{(glycylamino)methyl}piperidine was also synthesized pursuant to methods of Reference Example 25 using the corresponding reactant: 333 mg, 79%.

Reference Example 27: Preparation of 4-{(glycylamino)methyl}-1-(4-fluorobenzyl)piperidine.

A solution of 4-[{*N*-(9-fluorenylmethyloxycarbonyl)glycyl}aminomethyl]piperidine (1.50 g, 3.49 mmol), 4-fluorobenzyl bromide (0.478 mL, 3.84 mmol), and Et_3N (1.47 mL, 10.5 mmol) in CH_3CN (200 mL) was stirred at room temperature for 13 h and concentrated. Column chromatography (SiO2, 10% CH_3OH/CH_2Cl_2) afforded 4-[{*N*-(9-

fluorenylmethyloxycarbonyl)glycyl}aminomethyl]-1-(4-fluorobenzyl)piperidine.

A solution of the 4-[{*N*-(9-fluorenylmethyloxycarbonyl)glycyl}aminomethyl]-1-(4-fluorobenzyl)piperidine and piperidine (5 mL) in DMF (5 mL) was stirred at room temperature for 17 h. Concentration and column chromatography (SiO_2, Et_3N : CH_3OH : CH_2Cl_2 = 0.5: 2 : 8) afforded 4-{(glycylamino)methyl}-1-(4-fluorobenzyl)piperidine (453 mg, 46%).

Reference Example 28: Preparation of 4-{(glycylamino)methyl}-1-{4-(*N*-phenylcarbamoyl)benzyl}piperidine.

To a mixture of 4-[{*N*-(9-fluorenylmethyloxycarbonyl)glycyl}aminomethyl]piperidine (1.27 g, 2.96 mmol), Et_3N (1.25 mL, 8.88 mmol), KI (50 mg, 0.30 mmol) and CH_3CN (200 mL) was added dropwise a solution of 4-(*N*-phenylcarbamoyl)benzyl chloride (800 mg, 3.26 mmol) in CH_3CN (100 mL). The mixture was stirred at room temperature for 19 h and at 60 °C for 5 h. Concentration and column chromatography (SiO_2, 5% CH_3OH/CH_2Cl_2-Et_3N : CH_3OH : CH_2Cl_2 = 2 : 2 : 96) afforded 4-{(glycylamino)methyl}-1-{4-(*N*-phenylcarbamoyl)benzyl}piperidine (340 mg, 30%).

Example 1091: Preparation of 1-(4-Chlorobenzyl)-4-[{*N*-(3-cyanobenzoyl)valyl}aminomethyl]piperidine (Compound No. 619).

A solution of 1-(4-chlorobenzyl)-4-{(valylamino)methyl}piperidine (20 mg, 0.059 mmol) in CH_2Cl_2 (0.60 mL) was treated with Et_3N (0.011 mL, 0.077 mmol), *m*-cyanobenzoic acid (28 mg, 0.071 mmol), EDCI (13 mg, 0.065 mmol) and HOBt (9 mg, 0.065 mmol). The reaction mixture was stirred at 25 °C for 16 h. The resulting solution was diluted with CH_2Cl_2 (0.75 mL), washed with 2 N aqueous NaOH solution (2 x 0.75 mL) and dried by filtration through a PTFE membrane. Concentration afforded the 1-(4-chlorobenzyl)-4-[{N-(3-cyanobenzoyl)valyl}aminomethyl]piperidine (compound No. **619**) (24.2 mg, 88%) which required no further purification: The purity was determined by RPLC/MS (85%); ESI/MS m/e 467 (M^++H, $C_{26}H_{31}ClN_4O_2$).

Examples 1092-1543.

The compounds of this invention were synthesized pursuant to methods of Example 1091 using the corresponding reactant respectively. The ESI/MS data and yields are summarized in Table 27.

Table 27

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 1092	467	C22 H25 Br Cl N3 O2	478	11	46
Example 1093	468	C24 H31 Cl N4 O2	443	9	41
Example 1094	469	C23 H28 Cl N3 O3	430	7*	27
Example 1095	470	C23 H25 Cl N4 O2	425	21	quant
Example 1096	471	C24 H28 Cl N3 O4	458	7	29
Example 1097	472	C29 H31 N3 O3	504	5*	21
Example 1098	473	C24 H28 Cl N3 O3	442	16	71
Example 1099	474	C23 H25 Cl F3 N3 O2	468	14	60
Example 1100	475	C25 H32 Cl N3 O2	442	5	22
Example 1101	476	C22 H25 Cl N4 O4	445	4	17
Example 1102	477	C25 H32 Cl N3 O3	458	10*	36
Example 1103	478	C21 H27 Cl N4 O2	403	9	47
Example 1104	479	C20 H24 Cl N3 O3	390	17	87
Example 1105	480	C20 H23 Br Cl N3 O3	470	23	quant
Example 1106	481	C20 H24 Cl N3 O2 S	406	7	33
Example 1107	482	C21 H26 Cl N3 O2 S	420	9	45
Example 1108	483	C21 H26 Cl N3 O2 S	420	8	40
Example 1109	484	C24 H27 Cl N4 O2	439	9*	34
Example 1110	485	C24 H24 Cl F6 N3 O2	536	13	49
Example 1111	486	C23 H25 Cl N4 O2	425	16	74
Example 1112	487	C22 H25 Cl2 N3 O2	434	5	24
Example 1113	488	C22 H27 Cl N4 O2	415	7	32
Example 1114	489	C24 H24 Cl F6 N3 O2	536	21	78
Example 1115	490	C24 H30 Cl N3 O3	444	8	35
Example 1116	491	C23 H24 Cl F4 N3 O2	486	19	79
Example 1117	492	C23 H25 Cl F3 N3 O3	484	18	76
Example 1118	493	C23 H24 Cl2 F3 N3 O2	502	23	92
Example 1119	494	C23 H24 Cl F4 N3 O2	486	19	79
Example 1120	495	C23 H24 Cl F4 N3 O2	486	20	83
Example 1121	496	C23 H24 Cl F4 N3 O2	486	12	48
Example 1122	497	C25 H32 Cl N3 O3	458	4	16
Example 1123	498	C23 H26 Cl F3 N4 O2	483	13	52
Example 1124	499	C24 H31 Cl N4 O2	443	8	36
Example 1125	500	C23 H28 Cl N3 O3	430	10	48
Example 1126	501	C22 H24 Br Cl N4 O4	523	10	39
Example 1127	502	C22 H24 Cl F N4 O4	463	4	17

Example 1128	503	C22 H24 Cl2 N4 O4	479	12	52
Example 1129	504	C24 H30 Cl N3 O4	460	11	43
Example 1130	505	C22 H24 Br Cl N4 O4	523	2	8
Example 1131	506	C20 H23 Cl N4 O5	435	2	10
Example 1132	507	C21 H26 Cl N3 O3	404	9	44
Example 1133	508	C24 H26 Cl N3 O2 S	456	1	5
Example 1134	509	C20 H23 Br Cl N3 O2 S	484	12	48
Example 1135	510	C22 H28 Cl N3 O3	418	9	44
Example 1136	511	C24 H32 Cl N3 O3	446	9	40
Example 1137	512	C25 H29 Cl N4 O2	453	10	45
Example 1138	513	C24 H28 Cl N3 O3	442	9	41
Example 1139	514	C26 H34 Cl N3 O2	456	11	49
Example 1140	515	C23 H28 Cl N3 O3	430	5	24
Example 1141	525	C23 H28 Cl N3 O4 S	478	20	85
Example 1142	526	C20 H24 Cl N3 O3	390	6	31
Example 1143	527	C20 H24 Cl N3 O2 S	406	8	39
Example 1144	528	C25 H30 Cl F3 N4 O4	543	28.2	95
Example 1145	529	C20 H23 Cl N4 O4 S	451	9	39
Example 1146	530	C31 H33 Cl N4 O2	529	5	17
Example 1147	531	C21 H26 Cl N3 O3 S	436	8	37
Example 1148	532	C22 H28 Cl N3 O3	418	8	40
Example 1149	533	C21 H26 Cl N3 O3	404	6	32
Example 1150	534	C21 H25 Cl N4 O5	449	5	20
Example 1151	535	C22 H26 Cl N3 O3 S	448	8	37
Example 1152	536	C23 H31 Cl N4 O2	431	6	28
Example 1153	537	C25 H34 Cl N3 O3	460	8	34
Example 1154	538	C27 H30 Cl N3 O3	480	9	36
Example 1155	539	C22 H25 Cl F3 N3 O3	472	18	75
Example 1156	540	C25 H29 Cl N4 O2	453	8	36
Example 1157	541	C22 H26 Cl N5 O4	460	2.4	10
Example 1158	542	C24 H30 Cl N3 O2	428	4.6*	51
Example 1159	543	C24 H30 Cl N3 O2	428	20.6*	71
Example 1160	544	C22 H25 Cl F N3 O2	418	15.8*	56
Example 1161	545	C22 H24 Cl3 N3 O2	468	7.3*	23
Example 1162	546	C22 H24 Cl3 N3 O2	468	17.4*	55
Example 1163	547	C22 H24 Cl3 N3 O2	468	14.1*	44
Example 1164	548	C22 H24 Cl3 N3 O2	468	6.8*	22
Example 1165	549	C22 H24 Cl2 N4 O4	479	5.7*	18
Example 1166	550	C22 H24 Cl2 N4 O4	479	18.9*	58
Example 1167	551	C24 H30 Cl N3 O2	428	14.2*	49

Example 1168	552	C24 H27 Cl F3 N3 O2	482	30.6*	94
Example 1169	553	C25 H26 Cl F6 N3 O2	550	38.0*	quant
Example 1170	554	C24 H26 Cl F N4 O2	457	0.9*	3
Example 1171	555	C24 H26 Cl2 N4 O2	473	11.1*	35
Example 1172	556	C25 H29 Cl N4 O2	453	12.5*	41
Example 1173	559	C25 H26 Cl F6 N3 O2	550	15	72
Example 1174	560	C24 H27 Cl N4 O2	439	12	68
Example 1175	561	C23 H27 Br Cl N3 O2	494	14	73
Example 1176	562	C23 H27 Cl2 N3 O2	448	13	75
Example 1177	563	C25 H26 Cl F6 N3 O2	550	14	66
Example 1178	564	C25 H32 Cl N3 O3	458	5	28
Example 1179	565	C24 H26 Cl F4 N3 O2	500	12	61
Example 1180	566	C24 H27 Cl F3 N3 O3	498	12	62
Example 1181	567	C24 H26 Cl2 F3 N3 O2	516	12	61
Example 1182	568	C24 H26 Cl F4 N3 O2	500	15	77
Example 1183	569	C24 H26 Cl F4 N3 O2	500	11	59
Example 1184	570	C24 H26 Cl F4 N3 O2	500	16	84
Example 1185	571	C26 H34 Cl N3 O3	472	14	77
Example 1186	572	C24 H28 Cl F3 N4 O2	497	11	55
Example 1187	573	C21 H25 Br Cl N3 O2 S	500	12	64
Example 1188	574	C21 H25 Br Cl N3 O2 S	500	15	75
Example 1189	575	C25 H34 Cl N3 O3	460	16	87
Example 1190	576	C22 H28 Cl N3 O2 S2	466	13	71
Example 1191	577	C22 H28 Cl N3 O3	418	12	72
Example 1192	578	C25 H28 Cl N3 O2 S	470	15	81
Example 1193	579	C25 H29 Cl N4 O2	453	17	94
Example 1194	580	C22 H28 Cl N3 O2 S	434	15	91
Example 1195	581	C21 H26 Cl N3 O2 S	420	13	80
Example 1196	582	C22 H28 Cl N3 O2 S	434	10	59
Example 1197	583	C26 H31 Cl N4 O2	467	6	31
Example 1198	584	C30 H32 Cl N3 O3	518	18	92
Example 1199	585	C24 H27 Cl N4 O2	439	14	85
Example 1200	586	C23 H27 Cl2 N3 O2	448	17	97
Example 1201	587	C24 H27 Cl F3 N3 O2	482	17	91
Example 1202	588	C23 H29 Cl N4 O2	429	5	29
Example 1203	589	C27 H36 Cl N3 O2	470	4	24
Example 1204	590	C26 H34 Cl N3 O2	456	6	36
Example 1205	591	C25 H33 Cl N4 O2	457	7	38
Example 1206	592	C24 H30 Cl N3 O3	444	4	20
Example 1207	593	C24 H30 Cl N3 O3	444	2	14

Example 1208	594	C23 H28 Cl N3 O3	430	4	25
Example 1209	595	C25 H30 Cl N3 O4	472	7	38
Example 1210	596	C25 H30 Cl N3 O3	456	7	40
Example 1211	597	C25 H30 Cl N3 O3	456	15	85
Example 1212	598	C21 H26 Cl N3 O3	404	15	94
Example 1213	599	C22 H29 Cl N4 O2	417	5	30
Example 1214	600	C21 H25 Br Cl N3 O3	484	6	34
Example 1215	601	C24 H30 Cl N3 O3	444	5	28
Example 1216	602	C25 H33 Cl N4 O2	457	5	28
Example 1217	603	C23 H29 Cl N4 O2	429	4	22
Example 1218	604	C21 H27 Cl N4 O2	403	9	58
Example 1219	605	C21 H26 Cl N3 O3	404	17	87
Example 1220	606	C21 H26 Cl N3 O2 S	420	15	74
Example 1221	607	C22 H28 Cl N3 O3 S	450	31	quant
Example 1222	608	C23 H30 Cl N3 O3	432	17	80
Example 1223	609	C22 H28 Cl N3 O3	418	18	89
Example 1224	610	C23 H28 Cl N3 O3 S	462	20	86
Example 1225	611	C26 H36 Cl N3 O3	474	21	90
Example 1226	612	C28 H32 Cl N3 O3	494	20	84
Example 1227	613	C23 H27 Cl F3 N3 O3	486	19	81
Example 1228	614	C24 H33 Cl N4 O2	445	23	quant
Example 1229	615	C25 H29 Cl N4 O2	453	4	20
Example 1230	616	C32 H35 Cl N4 O2	543	11	40
Example 1231	617	C25 H27 Cl F3 N3 O2	482	6.7	37
Example 1232	620	C25 H31 Br Cl N3 O2	520	15	49
Example 1233	621	C25 H31 Cl2 N3 O2	476	18	64
Example 1234	622	C27 H37 Cl N4 O2	485	14	50
Example 1235	623	C26 H34 Cl N3 O3	472	19	69
Example 1236	624	C25 H31 Cl N4 O4	487	21	73
Example 1237	625	C25 H33 Cl N4 O2	457	19	69
Example 1238	626	C27 H30 Cl F6 N3 O2	578	8	25
Example 1239	627	C27 H36 Cl N3 O3	486	16	55
Example 1240	628	C27 H34 Cl N3 O4	500	24	80
Example 1241	629	C26 H30 Cl F4 N3 O2	528	18	56
Example 1242	630	C26 H31 Cl F3 N3 O3	526	21	68
Example 1243	631	C26 H30 Cl2 F3 N3 O2	544	15	48
Example 1244	632	C26 H30 Cl F4 N3 O2	528	13	41
Example 1245	633	C26 H30 Cl F4 N3 O2	528	20	63
Example 1246	634	C26 H30 Cl F4 N3 O2	528	19	62
Example 1247	635	C28 H38 Cl N3 O3	500	11	36

Example 1248	636	C26 H34 Cl N3 O2	456	21	89
Example 1249	637	C26 H31 Cl F3 N3 O2	510	20	95
Example 1250	638	C26 H31 Cl N4 O2	467	15	54
Example 1251	639	C27 H37 Cl N4 O2	485	19	66
Example 1252	640	C26 H34 Cl N3 O3	472	16	56
Example 1253	641	C27 H34 Cl N3 O4	500	18	59
Example 1254	642	C32 H36 Cl N3 O3	546	24	73
Example 1255	643	C26 H31 Cl F3 N3 O2	510	16	54
Example 1256	644	C29 H40 Cl N3 O2	498	18	61
Example 1257	645	C25 H33 Cl N4 O2	457	22	78
Example 1258	646	C26 H34 Cl N3 O3	472	13	47
Example 1259	647	C27 H34 Cl N3 O3	500	13	46
Example 1260	648	C28 H38 Cl N3 O2	484	17	60
Example 1261	649	C28 H38 Cl N3 O3	500	12.5	42
Example 1262	650	C32 H36 Cl N3 O3	546	1*	2
Example 1263	651	C28 H35 Cl N4 O2	495	4*	12
Example 1264	652	C25 H31 Cl N4 O4	487	5*	14
Example 1265	653	C30 H42 Cl N3 O3	528	1*	3
Example 1266	654	C27 H34 Cl N3 O3	484	7*	21
Example 1267	655	C26 H32 Cl F3 N4 O2	525	6*	16
Example 1268	656	C23 H30 Cl N3 O3	432	6*	18
Example 1269	657	C23 H30 Cl N3 O2 S	448	4*	13
Example 1270	658	C27 H33 Cl N4 O2	48	1*	4
Example 1271	659	C23 H29 Cl N4 O4 S	493	4*	10
Example 1272	660	C34 H39 Cl N4 O2	571	3*	7
Example 1273	661	C24 H32 Cl N3 O3 S	478	3*	7
Example 1274	662	C25 H34 Cl N3 O3	460	2*	6
Example 1275	663	C24 H32 Cl N3 O3	446	2*	5
Example 1276	664	C24 H31 Cl N4 O5	491	2*	5
Example 1277	665	C25 H32 Cl N3 O3 S	490	1*	3
Example 1278	666	C26 H37 Cl N4 O2	473	3*	7
Example 1279	667	C30 H36 Cl N3 O3	522	3*	7
Example 1280	668	C25 H31 Cl F3 N3 O3	514	2*	6
Example 1281	669	C24 H33 Cl N4 O2	445	15*	45
Example 1282	670	C23 H29 Br Cl N3 O3	510	3*	7
Example 1283	671	C23 H29 Cl N4 O5	477	2*	5
Example 1284	672	C23 H31 Cl N4 O2	431	2*	7
Example 1285	673	C23 H30 Cl N3 O2 S	448	2*	6
Example 1286	674	C24 H32 Cl N3 O2 S	462	3*	9
Example 1287	675	C24 H32 Cl N3 O2 S	462	1*	4

Example 1288	676	C27 H33 Cl N4 O2	482	2*	6
Example 1289	677	C28 H35 Cl N4 O2	495	2*	6
Example 1290	678	C24 H32 Cl N3 O3	446	3*	9
Example 1291	679	C27 H32 Cl N3 O2 S	498	1*	3
Example 1292	680	C23 H29 Br Cl N3 O2 S	526	2*	6
Example 1293	681	C25 H34 Cl N3 O3	460	2*	5
Example 1294	682	C27 H38 Cl N3 O3	488	2*	4
Example 1295	683	C24 H32 Cl N3 O2 S2	494	1*	4
Example 1296	684	C26 H36 Cl N3 O4 S2	554	2*	5
Example 1297	685	C24 H32 Cl N3 O4 S2	526	3*	7
Example 1298	687	C25 H30 Cl N3 O2	440	24	quant
Example 1299	688	C27 H28 Cl F6 N3 O2	576	28	98
Example 1300	689	C26 H29 Cl N4 O2	465	23	99
Example 1301	690	C25 H29 Br Cl N3 O2	518	26	99
Example 1302	691	C27 H35 Cl N4 O2	483	24	97
Example 1303	692	C26 H32 Cl N3 O3	470	24	quant
Example 1304	693	C27 H28 Cl F6 N3 O2	576	16	55
Example 1305	694	C27 H34 Cl N3 O3	484	25	quant
Example 1306	695	C27 H32 Cl N3 O4	498	12	47
Example 1307	696	C26 H29 Cl F3 N3 O3	524	25	95
Example 1308	697	C26 H29 Cl N4 O2	465	15	64
Example 1309	698	C27 H35 Cl N4 O2	483	24	quant
Example 1310	699	C26 H32 Cl N3 O3	470	26	quant
Example 1311	700	C27 H32 Cl N3 O4	498	15	62
Example 1312	701	C27 H32 Cl N3 O3	482	11	44
Example 1313	702	C26 H29 Cl F3 N3 O2	508	23	94
Example 1314	703	C28 H36 Cl N3 O2	482	26	quant
Example 1315	704	C25 H29 Cl N4 O4	485	11	43
Example 1316	705	C24 H30 Cl N3 O2 S	460	25	quant
Example 1317	706	C24 H30 Cl N3 O2 S	460	25	quant
Example 1318	707	C26 H29 Cl F3 N3 O2	508	15	55
Example 1319	708	C23 H27 Br Cl N3 O2 S	526	25	92
Example 1320	709	C24 H30 Cl N3 O2 S2	492	26	quant
Example 1321	710	C23 H27 Br Cl N3 O2 S	526	25	94
Example 1322	711	C25 H32 Cl N3 O3	458	26	quant
Example 1323	712	C27 H30 Cl N3 O2 S	496	26	quant
Example 1324	713	C24 H30 Cl N3 O3	444	26	quant
Example 1325	714	C28 H33 Cl N4 O2	493	12	50
Example 1326	715	C23 H28 Cl N3 O2 S	446	24	quant
Example 1327	716	C27 H31 Cl N4 O2	479	32	quant

Example 1328	717	C23 H27 Cl N4 O5	475	23	95
Example 1329	718	C23 H29 Cl N4 O2	429	24	quant
Example 1330	719	C23 H28 Cl N3 O3	430	24	quant
Example 1331	720	C23 H27 Br Cl N3 O3	510	24	95
Example 1332	721	C24 H31 Cl N4 O2	443	22	98
Example 1333	722	C26 H32 Cl N3 O3	470	9	37
Example 1334	723	C25 H31 Cl N4 O2	455	10	44
Example 1335	724	C29 H38 Cl N3 O2	496	28	quant
Example 1336	725	C32 H34 Cl N3 O3	544	26	95
Example 1337	726	C27 H33 Cl N4 O3	497	3	11
Example 1338	727	C25 H29 Cl2 N3 O2	474	25	quant
Example 1339	728	C25 H31 Cl N4 O2	455	21	92
Example 1340	729	C25 H29 Cl N4 O4	485	26	quant
Example 1341	730	C25 H29 Cl2 N3 O2	474	21	90
Example 1342	731	C27 H32 Cl N3 O3	482	10	41
Example 1343	732	C26 H28 Cl F4 N3 O2	526	27	quant
Example 1344	733	C28 H36 Cl N3 O3	498	22	89
Example 1345	734	C26 H28 Cl F4 N3 O2	526	25	94
Example 1346	735	C26 H28 Cl F4 N3 O2	526	23	87
Example 1347	736	C26 H30 Cl F3 N4 O2	523	24	78
Example 1348	737	C26 H28 Cl F4 N3 O2	526	21	66
Example 1349	738	C25 H32 Cl N3 O3	458	23	84
Example 1350	739	C27 H31 Cl N4 O2	479	19	66
Example 1351	740	C24 H31 Cl N4 O5	489	23	77
Example 1352	741	C23 H27 Cl N4 O4 S	491	26	88
Example 1353	742	C24 H30 Cl N3 O3 S	476	23	82
Example 1354	743	C23 H28 Cl N3 O3	430	21	81
Example 1355	744	C26 H32 Cl N3 O2	454	25	91
Example 1356	745	C27 H36 Cl N3 O3	486	23	80
Example 1357	746	C26 H35 Cl N4 O2	471	27	96
Example 1358	747	C25 H29 Cl F3 N3 O3	512	23	74
Example 1359	748	C23 H28 Cl N3 O2 S	446	22	82
Example 1360	751	C24 H30 Cl N3 O3	444	3	11
Example 1361	752	C25 H26 Cl F6 N3 O3	566	7	20
Example 1362	753	C24 H27 Cl N4 O3	455	6	22
Example 1363	754	C23 H27 Cl2 N3 O3	464	8	29
Example 1364	755	C24 H30 Cl N3 O4	460	6	22
Example 1365	756	C23 H27 Cl N4 O5	475	5	18
Example 1366	757	C25 H32 Cl N3 O4	474	5	18
Example 1367	758	C25 H30 Cl N3 O5	488	5	18

Example 1368	759	C24 H27 Cl F3 N3 O4	514	6	20
Example 1369	760	C24 H26 Cl F4 N3 O3	516	6	18
Example 1370	761	C24 H26 Cl F4 N3 O3	516	3	10
Example 1371	762	C24 H27 Cl F3 N3 O3	498	2	95
Example 1372	763	C23 H28 Cl N3 O3	430	4	95
Example 1373	764	C24 H30 Cl N3 O2	428	9	42
Example 1374	765	C25 H32 Cl N3 O2	442	10	47
Example 1375	766	C25 H29 Cl F3 N3 O2	496	10	42
Example 1376	767	C25 H32 Cl N3 O4 S	506	8	32
Example 1377	768	C24 H29 Br Cl N3 O2	506	9	35
Example 1378	769	C25 H29 Cl F3 N3 O3	512	6	22
Example 1379	770	C25 H28 Cl F4 N3 O2	514	3	10
Example 1380	771	C25 H28 Cl F4 N3 O2	514	10	37
Example 1381	772	C25 H29 Cl F3 N3 O2	496	8	33
Example 1382	773	C26 H36 Cl N3 O3	474	10	41
Example 1383	774	C23 H30 Cl N3 O2 S2	480	12	50
Example 1384	775	C27 H38 Cl N3 O3	488	14	57
Example 1385	776	C29 H34 Cl N3 O3	508	12	49
Example 1386	777	C24 H29 Cl F3 N3 O3	500	22	87
Example 1387	778	C24 H28 Cl2 N4 O4	507	6	22
Example 1388	779	C24 H29 Cl2 N3 O2	462	10	46
Example 1389	780	C24 H29 Cl N4 O4	473	15	65
Example 1390	781	C26 H31 Cl N4 O2	467	7*	20
Example 1391	782	C25 H32 Cl N3 O3	458	8*	23
Example 1392	783	C26 H34 Cl N3 O3	472	7*	19
Example 1393	784	C26 H31 Cl F3 N3 O2	510	7*	17
Example 1394	785	C26 H34 Cl N3 O4	488	6*	17
Example 1395	786	C24 H28 Cl N3 O2	426	22	9
Example 1396	787	C25 H30 Cl N3 O2	440	21	94
Example 1397	788	C25 H27 Cl F3 N3 O2	494	4*	14
Example 1398	789	C25 H30 Cl N3 O4 S	504	9	35
Example 1399	790	C24 H27 Cl2 N3 O2	460	5*	16
Example 1400	791	C24 H27 Cl N4 O4	471	3*	10
Example 1401	792	C25 H27 Cl F3 N3 O3	510	5*	16
Example 1402	793	C25 H26 Cl F4 N3 O2	511	5*	16
Example 1403	794	C25 H26 Cl F4 N3 O2	512	5*	16
Example 1404	795	C25 H27 Cl F3 N3 O2	494	6*	21
Example 1405	796	C23 H28 Cl N3 O2 S2	478	4*	14
Example 1406	797	C27 H36 Cl N3 O3	486	7*	29
Example 1407	798	C29 H32 Cl N3 O3	506	3	13

Example 1408	799	C24 H27 Cl F3 N3 O3	498	3*	11
Example 1409	800	C24 H26 Cl2 N4 O4	505	5*	15
Example 1410	801	C26 H29 Cl N4 O2	465	12	41
Example 1411	802	C25 H30 Cl N3 O3	456	5*	15
Example 1412	803	C26 H32 Cl N3 O3	470	6*	16
Example 1413	804	C26 H29 Cl F3 N3 O2	508	8*	20
Example 1414	805	C26 H32 Cl N3 O4	486	6*	15
Example 1415	806	C24 H27 Br Cl N3 O2	506	5*	14
Example 1416	807	C27 H32 Cl N5 O3	510	29.7	quant
Example 1417	808	C26 H33 Cl N4 O3	485	29.9	quant
Example 1418	809	C25 H30 Cl2 N4 O3	505	30.2	quant
Example 1419	810	C30 H35 Cl N4 O4	551	31.0	quant
Example 1420	811	C25 H29 Cl2 N5 O5	550	30.4	quant
Example 1421	812	C24 H31 Cl N4 O3 S2	523	25.0	88
Example 1422	813	C26 H30 Cl F3 N4 O3	539	20.5	70
Example 1423	814	C26 H30 Cl F3 N4 O4	555	22.7	75
Example 1424	815	C26 H29 Cl F4 N4 O3	557	25.8	85
Example 1425	816	C26 H30 Cl F3 N4 O3	539	25.3	86
Example 1426	817	C26 H29 Cl F4 N4 O3	557	26.8	88
Example 1427	818	C25 H30 Br Cl N4 O3	551	27.1	90
Example 1428	819	C27 H29 Cl F6 N4 O3	607	13.9	42
Example 1429	820	C25 H30 Cl N5 O5	516	14.1	51
Example 1430	821	C24 H28 Cl2 N4 O5	523	40	86
Example 1431	822	C23 H30 Cl N3 O3 S2	496	41	93
Example 1432	823	C26 H31 Cl N4 O3	483	43	quant
Example 1433	824	C27 H38 Cl N3 O4	503	37	83
Example 1434	825	C29 H34 Cl N3 O4	524	28	61
Example 1435	826	C24 H29 Cl F3 N3 O4	516	40	87
Example 1436	827	C26 H31 Cl N4 O3	483	31	72
Example 1437	828	C25 H29 Cl F3 N3 O4	528	40	86
Example 1438	829	C25 H28 Cl F4 N3 O3	530	45	97
Example 1439	830	C25 H28 Cl F4 N3 O3	530	35	74
Example 1440	831	C24 H29 Br Cl N3 O3	523	45	98
Example 1441	832	C24 H29 Cl2 N3 O3	478	38	91
Example 1442	833	C24 H29 Cl N4 O5	488	38	87
Example 1443	834	C25 H29 Cl F3 N3 O3	512	42	93
Example 1444	835	C24 H30 Cl N3 O3	444	43	quant
Example 1445	836	C25 H32 Cl N3 O3	458	37	91
Example 1446	837	C25 H29 Cl F3 N3 O3	512	41	91
Example 1447	838	C26 H34 Cl N3 O4	488	34	78

Example 1448	839	C27 H36 Cl N3 O6	534	37	71
Example 1449	942	C27 H30 Cl F6 N3 O2	578	17	48
Example 1450	997	C26 H34 Cl N3 O2	456	7.6*	23
Example 1451	998	C27 H33 Cl F3 N3 O2	524	6	15
Example 1452	999	C27 H36 Cl N3 O2	470	8	24
Example 1453	1000	C27 H36 Cl N3 O3	486	9	24
Example 1454	1001	C28 H38 Cl N3 O3	500	4	10
Example 1455	1002	C27 H33 Cl F3 N3 O3	540	9	23
Example 1456	1003	C28 H38 Cl N3 O2	484	7	21
Example 1457	1004	C28 H38 Cl N3 O4	516	11	30
Example 1458	1005	C29 H40 Cl N3 O5	547	9	23
Example 1459	1006	C30 H42 Cl N3 O4	544	8	21
Example 1460	1007	C32 H46 Cl N3 O5	589	7	17
Example 1461	1008	C25 H31 Cl N4 O3	471	25	79
Example 1462	1009	C26 H33 Cl N4 O4	501	35	97
Example 1463	1010	C27 H35 Cl N4 O4	515	35	9
Example 1464	1011	C27 H35 Cl N4 O3	499	32	54
Example 1465	1012	C27 H35 Cl N4 O5	531	27	77
Example 1466	1013	C28 H37 Cl N4 O6	561	14	37
Example 1467	1014	C29 H39 Cl N4 O5	559	24	66
Example 1468	1015	C31 H43 Cl N4 O6	603	25	65
Example 1469	1018	C26 H34 Cl N3 O4	488	13.0*	39
Example 1470	1019	C28 H38 Cl N3 O5	532	13.4*	37
Example 1471	1020	C25 H32 Cl N3 O4	474	12.7*	40
Example 1472	1021	C26 H28 Cl F6 N3 O4	596	13.8*	34
Example 1473	1022	C25 H32 Cl N3 O4	474	14.2*	37
Example 1474	1023	C25 H32 Cl N3 O2	442	11.5*	32
Example 1475	1024	C26 H34 Cl N3 O5	504	12.0*	30
Example 1476	1025	C27 H36 Cl N3 O4	502	14.7*	37
Example 1477	1026	C29 H40 Cl N3 O5	546	13.5*	32
Example 1478	1027	C26 H34 Cl N3 O4	488	11.9*	31
Example 1479	1028	C27 H30 Cl F6 N3 O4	610	14.6*	31
Example 1480	1029	C25 H32 Cl N3 O3	458	14.0*	38
Example 1481	1030	C24 H27 Cl F3 N3 O3	498	14.0*	35
Example 1482	1031	C24 H30 Cl N3 O3	444	10.4*	29
Example 1483	1032	C25 H32 Cl N3 O4	474	14.9*	39
Example 1484	1033	C25 H32 Cl N3 O2	442	13.3*	37
Example 1485	1034	C26 H34 Cl N3 O5	504	13.7*	34
Example 1486	1035	C27 H36 Cl N3 O4	502	16.7*	42
Example 1487	1036	C29 H40 Cl N3 O5	547	15.5*	36

Example 1488	1037	C26 H34 Cl N3 O4	488	14.1*	36
Example 1489	1038	C27 H30 Cl F6 N3 O4	610	17.5*	37
Example 1490	1039	C25 H32 Cl N3 O3	458	15.1*	41
Example 1491	1040	C24 H27 Cl F3 N3 O3	498	15.4*	39
Example 1492	1041	C24 H30 Cl N3 O3	444	12.7*	35
Example 1493	1042	C22 H26 Br Cl N4 O2	495	10.4*	25
Example 1494	1043	C22 H26 Cl2 N4 O2	449	11.1*	29
Example 1495	1044	C23 H29 Cl N4 O2	429	5.2*	14
Example 1496	1045	C23 H29 Cl N4 O3	445	12.4*	33
Example 1497	1046	C22 H25 Cl3 N4 O2	483	10.0*	25
Example 1498	1047	C24 H31 Cl N4 O2	443	12.1*	32
Example 1499	1048	C25 H33 Cl N4 O5	505	16.1*	39
Example 1500	1049	C23 H28 Br Cl N4 O2	507	12.0*	29
Example 1501	1050	C28 H38 Cl N3 O4	516	39.2*	quant
Example 1502	1051	C28 H38 Cl N3 O2	484	34.0*	quant
Example 1503	1052	C29 H40 Cl N3 O5	546	14.5*	39
Example 1504	1053	C30 H42 Cl N3 O4	544	11.8*	32
Example 1505	1054	C32 H46 Cl N3 O5	588	12.2*	31
Example 1506	1055	C29 H40 Cl N3 O4	530	44.5*	quant
Example 1507	1056	C30 H36 Cl F6 N3 O4	652	46.0*	quant
Example 1508	1057	C28 H38 Cl N3 O3	500	11.2*	32
Example 1509	1058	C27 H36 Cl N3 O3	486	35.5*	quant
Example 1510	1059	C27 H33 Cl F3 N3 O3	540	41.4*	quant
Example 1511	1060	C29 H40 Cl N3 O4	530	13.6*	37
Example 1512	1061	C30 H36 Cl F6 N3 O4	652	44.2*	quant
Example 1513	1062	C28 H38 Cl N3 O3	500	39.9*	quant
Example 1514	1063	C27 H36 Cl N3 O3	486	12.0*	35
Example 1515	1064	C27 H33 Cl F3 N3 O3	540	37.8*	quant
Example 1516	1065	C28 H38 Cl N3 O4	516	12.3*	34
Example 1517	1066	C28 H38 Cl N3 O2	484	30.7*	90
Example 1518	1067	C29 H40 Cl N3 O5	546	13.8*	37
Example 1519	1068	C30 H42 Cl N3 O4	544	13.1*	35
Example 1520	1069	C32 H46 Cl N3 O5	589	14.1*	35
Example 1521	1070	C29 H34 Cl N3 O3 S2	572	38.3	93
Example 1522	1071	C32 H35 Cl N4 O3	559	39.6	98
Example 1523	1072	C33 H42 Cl N3 O4	580	40.9	98
Example 1524	1073	C35 H38 Cl N3 O4	600	40.5	94
Example 1525	1074	C30 H33 Cl F3 N3 O4	592	38.7	91
Example 1526	1075	C31 H33 Cl F3 N3 O4	604	38	87
Example 1527	1076	C30 H33 Cl N4 O5	565	38.5	94

Example 1528	1077	C31 H33 Cl F3 N3 O3	588	35.8	84
Example 1529	1078	C30 H34 Cl N3 O3	520	34.7	93
Example 1530	1079	C31 H36 Cl N3 O3	534	38.4	quant
Example 1531	1080	C32 H38 Cl N3 O4	564	39.3	97
Example 1532	1081	C33 H40 Cl N3 O6	610	45.5	quant
Example 1533	1082	C28 H36 Cl N3 O3	498	4.1*	10
Example 1534	1083	C28 H36 Cl N3 O3	498	6.4*	16
Example 1535	1125	C30 H32 Cl2 N4 O5	599	3.4*	8
Example 1536	1126	C30 H32 Br Cl N4 O5	644	3.4*	7
Example 1537	1127	C32 H35 Cl N4 O3	559	1.6*	4
Example 1538	1128	C31 H32 Cl F4 N3 O3	606	4.3*	10
Example 1539	1129	C31 H32 Cl F4 N3 O3	606	5.9*	14
Example 1540	1130	C30 H33 Br Cl N3 O3	599	5.7*	13
Example 1541	1131	C30 H33 Cl2 N3 O3	554	6.4*	16
Example 1542	1132	C31 H33 Cl F3 N3 O3	588	6.3*	15
Example 1543	1167	C27 H34 Cl N3 O3	484	1.8*	4

*Yield of TFA salt.

Example 1544: Preparation of 1-(4-Chlorobenzyl)-4-[{*N*-(3,5-bis(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine (Compound No. 1213).

A solution of 3,5-bis(trifluoromethyl)benzoyl chloride (0.058 mmol) in dichloromethane (1 mL) was added to a mixture of 1-(4-chlorobenzyl)-4-{(glycylamino)methyl}piperidine (0.050 mmol) and piperidinomethylpolystyrene (58 mg) in chloroform (0.2 mL) and dichloromethane (0.75 mL). After the reaction mixture was stirred at room temperature for 2 h, methanol (1.0 mL) was added and the mixture was stirred at room temperature for 30 min. The reaction mixture was loaded onto Varian™ SCX column, and washed with CH_3OH (16 mL). Product was eluted off using 2 N NH_3 in CH_3OH (6 mL) and concentrated to afford 1-(4-chlorobenzyl)-4-[{*N*-(3,5-bis(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine (Compound No. **1213**) (24.0 mg, 90%): The purity was determined by RPLC/MS (100%); ESI/MS m/e 536.2 (M^++H, $C_{24}H_{24}ClF_6N_3O_2$).

Examples 1545-1547.

The compounds of this invention were synthesized pursuant to methods of Example 1544 using the corresponding reactant respectively. The ESI/MS data and yields are summarized in Table 28.

Table 28

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 1545	1214	C23 H24 Cl F4 N3 O3	486.2	22.2	91
Example 1546	1215	C22 H24 Cl3 N3 O2	467.9	20.9	89
Example 1547	1216	C22 H24 Cl F2 N3 O2	436.0	19.3	89

Example 1548: Preparation of 4-[{*N*-(3-Bromo-4-methylbenzoyl)glycyl}aminomethyl]-1-(4-chlorobenzyl) piperidine (Compound No. 1113).

A solution of 1-(4-chlorobenzyl)-4-{(glycylamino)methyl}piperidine (0.050 mmol) in $CHCl_3$ (1.35 mL) and *tert*-butanol (0.15 mL) was treated with 3-bromo-4-methylbenzoic acid (0.060 mmol), diisopropylcarbodiimide (0.060 mmol), and HOBt (0.060 mmol). The reaction mixture was stirred at room temperature for 15 h. The mixture was loaded onto Varian™ SCX column, and washed with $CH_3OH/CHCl_3$ 1:1 (12 mL) and CH_3OH (12 mL). Product was eluted off using 2 N NH_3 in CH_3OH (5 mL) and concentrated to afford 4-[{*N*-(3-bromo-4-methylbenzoyl)glycyl}aminomethyl]-1-(4-chlorobenzyl) piperidine (Compound No. **1113**) (16.1 mg, 65%): The purity was determined by RPLC/MS (95%); ESI/MS m/e 494.0 ($C_{23}H_{27}BrClN_3O_2$).

Examples 1549-1619.

The compounds of this invention were synthesized pursuant to methods of Example 1548 using the corresponding reactant respectively. Preparative TLC, if needed, afforded the desired material. The ESI/MS data and yields are summarized in Table 29.

Compound No. **1422** was obtained as byproduct of Compound No. **1418**: 5.6 mg, 25% yield; ESI/MS m/e 447.2 ($C_{22}H_{27}ClN_4O_2S$).

Table 29

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 1549	1114	$C_{22}H_{24}BrClFN_3O_2$	498.0	20.2	81
Example 1550	1115	$C_{22}H_{24}Cl_2FN_3O_2$	452.2	18.6	82
Example 1551	1116	$C_{23}H_{27}ClIN_3O_2$	539.1	21.9	81
Example 1552	1117	$C_{23}H_{27}ClN_4O_4$	459.2	18.7	81

Example 1553	1187	$C_{23}H_{27}BrClN_3O_2$	494.0	22.1	90
Example 1554	1188	$C_{24}H_{27}ClN_4O_3$	455.2	17.2	76
Example 1555	1189	$C_{25}H_{29}ClN_4O_3$	469.2	21.1	90
Example 1556	1190	$C_{22}H_{26}ClFN_4O_2$	433.2	20.4	94
Example 1557	1241	$C_{23}H_{24}Cl_2F_3N_3O_2$	502.0	22.5	90
Example 1558	1242	$C_{23}H_{27}ClFN_3O_2$	432.2	21.2	98
Example 1559	1243	$C_{23}H_{27}Cl_2N_3O_2$	448.0	21.6	96
Example 1560	1244	$C_{22}H_{26}ClIN_4O_2$	541.0	26.4	98
Example 1561	1245	$C_{22}H_{25}ClF_2N_4O_2$	451.0	21.3	94
Example 1562	1246	$C_{21}H_{27}ClN_4O_2$	403.2	19.4	96
Example 1563	1247	$C_{28}H_{30}ClN_3O_2S$	524.0	24.7	94
Example 1564	1248	$C_{22}H_{25}ClN_4O_5$	461.0	20.7	90
Example 1565	1282	$C_{25}H_{26}ClF_3N_4O_3$	523.2	25.0	96
Example 1566	1283	$C_{23}H_{27}Cl_2N_3O_3$	464.2	12.2	53
Example 1567	1284	$C_{22}H_{25}BrClN_3O_3$	496.0	24.1	97
Example 1568	1285	$C_{22}H_{25}Cl_2N_3O_3$	450.2	21.8	97
Example 1569	1342	$C_{22}H_{24}BrCl_2N_3O_2$	514.0	27.2	quant
Example 1570	1343	$C_{23}H_{27}Cl_2N_3O_2$	448.0	21.4	95
Example 1571	1344	$C_{22}H_{24}Cl_2IN_3O_2$	560.0	27.0	96
Example 1572	1345	$C_{23}H_{28}ClN_3O_2$	430.2	23.8	quant
Example 1573	1346	$C_{22}H_{25}ClIN_3O_3$	542.0	29.4	quant
Example 1574	1350	$C_{21}H_{26}ClN_3O_2S$	420.0	13.0	62
Example 1575	1354	$C_{24}H_{28}BrClN_4O_3$	537.2	5.2	19
Example 1576	1358	$C_{23}H_{26}ClN_5O_2$	440.2	21.8	99
Example 1577	1383	$C_{23}H_{24}Cl_2F_3N_3O_2$	502.0	20.0	80
Example 1578	1384	$C_{20}H_{23}BrClN_3O_2S$	486.0	21.0	87
Example 1579	1385	$C_{28}H_{30}ClN_3O_4S$	540.2	23.8	88
Example 1580	1386	$C_{28}H_{30}ClN_3O_2$	476.0	20.0	84
Example 1581	1414	$C_{24}H_{28}Cl_2N_4O_3$	491.0	0.8	3
Example 1582	1418	$C_{23}H_{26}ClN_5O_2S$	472.0	10.4	44
Example 1583	1436	C29 H30 Cl N3 O3	504.2	26.8	quant
Example 1584	1600	C23 H26 Cl F3 N4 O2	483.2	16.5	68
Example 1585	1601	C23 H26 Cl F3 N4 O3	499.0	20.0	80
Example 1586	1602	C21 H24 Br Cl N4 O2	481.0	18.1	75
Example 1587	1603	C21 H24 Cl2 N4 O2	435.0	5.5	25
Example 1588	1604	C27 H30 Cl N3 O3	492.0	18.6	76
Example 1589	1605	C21 H27 Cl N4 O2	415.2	18.1	87
Example 1590	1609	C23 H25 N3 O2 S	500.0	18.3	73
Example 1591	1659	C22 H26 Cl2 N4 O2	449.0	366.0	83
Example 1592	1664	C24 H29 F3 N4 O2 S	495.2	13.7	55

Example 1593	1665	C24 H29 F3 N4 O3 S	511.2	14.9	58
Example 1594	1666	C23 H28 F2 N4 O2 S	463.2	12.9	56
Example 1595	1667	C22 H27 Br2 N3 O3	542	26.1	96
Example 1596	1668	C24 H30 F2 N4 O2	445	22.9	quant
Example 1597	1669	C24 H31 F N4 O2	427	24.0	quant
Example 1598	1670	C24 H31 I N4 O2	535	28.1	quant
Example 1599	1671	C25 H31 F3 N4 O3	493	26.8	quant
Example 1600	1672	C25 H31 F3 N4 O2	478	24.7	quant
Example 1601	1673	C24 H29 Br Cl N3 O2	508	24.9	98
Example 1602	1674	C20 H22 Br2 F N3 O3	532	25.6	96
Example 1603	1675	C22 H25 F3 N4 O2	435	21.5	99
Example 1604	1676	C22 H26 F2 N4 O2	417	21.4	quant
Example 1605	1677	C22 H26 Br F N4 O2	479	23.4	98
Example 1606	1678	C22 H26 F I N4 O2	525	27.4	quant
Example 1607	1679	C22 H26 Cl F N4 O2	433	22.4	quant
Example 1608	1680	C23 H26 F4 N4 O3	483	25.5	quant
Example 1609	1681	C23 H26 F4 N4 O2	467	23.2	99
Example 1610	1682	C23 H26 Br Cl F N3 O	498	24.2	98
Example 1611	1683	C27 H28 Br2 N4 O4	633	31.8	quant
Example 1612	1684	C29 H31 F2 N5 O3	536	28.3	quant
Example 1613	1685	C29 H32 F N5 O3	518	31.1	quant
Example 1614	1686	C29 H32 Br N5 O3	578	29.6	quant
Example 1615	1687	C29 H32 I N5 O3	626	32.4	quant
Example 1616	1688	C29 H32 Cl N5 O3	534	28.2	quant
Example 1617	1689	C30 H32 F3 N5 O4	584	31.7	quant
Example 1618	1690	C30 H32 F3 N5 O3	568	30.6	quant
Example 1619	1691	C29 H30 Br Cl N4 O3	599	31.4	quant

For example, Compound **1245** and **1600** showed the following NMR spectra.

Compound No. **1245:** ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.20-1.97 (m, 7 H), 2.80-2.86 (m, 2 H), 3.19 (t, J = 6.5 Hz, 2 H), 3.43 (s, 2 H), 4.02 (d, J = 5.3 Hz, 2 H), 5.52 (br s, 2 H), 6.44 (d, J = 11.9, 6.6 Hz, 1 H), 7.02 (br s, 1 H), 7.21-7.32 (m, 5 H).

Compound No. **1600:** ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.25-1.97 (m, 9 H), 2.82-2.87 (m, 2 H), 3.21 (t, J = 6.5 Hz, 2 H), 3.44 (s, 2 H), 4.06 (d, J = 5.1 Hz, 2 H), 5.98 (br s, 1 H), 6.71 (d, J = 8.3 Hz, 1 H), 6.87 (br s, 1 H), 7.26 (s, 4 H), 7.43 (dd, J = 5.9 Hz, 1 H), 7.64 (s, 1 H).

Example 1620: Preparation of 1-(4-Chlorobenzyl)-4-[{*N*-(4-

isopropylphenylsulfonyl)glycyl}aminomethyl]piperidine (Compound No. 869).

A solution of 1-(4-chlorobenzyl)-4-{(glycylamino)methyl}piperidine (14.8 mg, 0.05 mmol) in $CHCl_3$ (2 mL) was treated with (piperidinomethyl)polystyrene resin (28 mg, 2.8 mmol/g), 4-isopropylbenzenesulfonyl chloride (1.5 equiv.) and stirred at 25 °C for 16 h. (Aminomethyl)polystyrene was added to scavenge the residual sulfonyl chloride and the reaction mixture was stirred at 25 °C for 16 h. Filtration and concentration afforded 1-(4-chlorobenzyl)-4-[{(4-isopropylphenylsulfonyl)glycyl}aminomethyl]piperidine (compound No. **869**) (22.1 mg, 92%): The purity was determined by RPLC/MS (86%); ESI/MS m/e 478 (M^++H, $C_{24}H_{32}ClN_3O_3S$).

Examples 1621-1627.

The compounds of this invention were synthesized pursuant to methods of Example 1620 using the corresponding reactant respectively. The ESI/MS data and yields are summarized in Table 30.

Table 30

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 1621	865	C22 H28 Cl N3 O3 S	450	16.2	72
Example 1622	866	C22 H25 Cl F3 N3 O3 S	504	8.8	35
Example 1623	867	C23 H24 Cl F6 N3 O3 S	572	8.0	28
Example 1624	868	C23 H30 Cl N3 O3 S	464	9.6	41
Example 1625	870	C22 H28 Cl N3 O3 S	450	8.8	39
Example 1626	871	C25 H34 Cl N3 O3 S	492	11.1	45
Example 1627	872	C21 H26 Cl N3 O3 S	436	9.6	44

Example 1628: Preparation of 1-(4-Chlorobenzyl)-4-[{2-(3-(4-trifluoromethylphenyl)ureido)acetylamino}methyl]piperidine (Compound No. 852).

A solution of 1-(4-chlorobenzyl)-4-{(glycylamino)methyl}piperidine (14.8 mg, 0.05 mmol) in $CHCl_3$ (2 mL) was treated with (piperidinomethyl)polystyrene resin (28 mg, 2.8 mmol/g), 3-(trifluoromethyl)phenyl isocyanate (1.3 equiv.) and stirred at 25 °C for 16 h. (Aminomethyl)polystyrene was added to scavenge the residual isocyanate and the reaction mixture was stirred at 25 °C for 16 h. Filtration and concentration

afforded 1-(4-chlorobenzyl)-4-[{2-(3-(4-trifluoromethylphenyl)ureido)acetylamino}methyl]piperidine (19 mg, 78%) (compound No. **852**): The purity was determined by RPLC/MS (92%); ESI/MS m/e 483 ($M^{+}+H$, $C_{23}H_{26}ClF_3N_4O_2$).

Examples 1629-1641.

The compounds of this invention were synthesized pursuant to methods of Example 1628 using the corresponding reactant respectively. The ESI/MS data and yields are summarized in Table 31.

Table 31

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 1629	851	C23 H26 Cl F3 N4 O2	483	13.2	55
Example 1630	853	C22 H27 Cl N4 O2	416	8.5*	32
Example 1631	854	C23 H29 Cl N4 O2	429	11.4*	42
Example 1632	855	C23 H29 Cl N4 O2	429	10.1*	37
Example 1633	856	C24 H29 Cl N4 O3	457	10.3*	36
Example 1634	857	C23 H29 Cl N4 O3	445	10.9*	39
Example 1635	858	C23 H29 Cl N4 O3	445	8.6*	31
Example 1636	859	C22 H26 Cl2 N4 O2	449	11.0*	39
Example 1637	860	C23 H26 Cl N5 O2	440	9.2*	33
Example 1638	861	C22 H27 Cl N4 O S	431	13.3	62
Example 1639	862	C23 H29 Cl N4 O S	445	15.3	69
Example 1640	863	C23 H29 Cl N4 O2 S	461	14.7	64
Example 1641	864	C23 H29 Cl N4 O2 S	461	13.1	57

*Yield of TFA salt.

Example 1642: Preparation of 1-(4-Chlorobenzyl)-4-[{*N*-(3-ethoxybenzoyl)-D-phenylalanyl}aminomethyl]piperidine (Compound No. 2091).

A solution of 1-(4-chlorobenzyl)-4-(aminomethyl)piperidine (100 mg) in $CHCl_3$ (3 mL) was treated with Et_3N (0.090 mL), *N*-(*tert*-butoxycarbonyl)-D-phenylalanine (122 mg), EDCI (89 mg) and HOBt (62 mg). The reaction mixture was stirred at room temperature for 17 h. The reaction mixture was washed with 1 N aqueous NaOH solution (2 mL x 2) and brine (2 mL). The organic layer was dried and concentrated to afford 1-(4-chlorobenzyl)-4-[{*N*-(*tert*-butoxycarbonyl)-D-phenylalanyl}aminomethyl]piperidine.

The resulting 1-(4-chlorobenzyl)-4-[{*N*-(*tert*-butoxycarbonyl)-D-

phenylalanyl}aminomethyl]piperidine was dissolved in methanol (5 mL) and 4 N HCl in dioxane (1.5 mL) was added. The solution was stirred at room temperature for 19 h and concentrated.

A solution of the resulting material and 3-ethoxybenzoic acid (80 mg, 0.48 mmol) in $CHCl_3$ (1 mL) was treated with Et_3N (0.090 mL), EDCI (90 mg) and HOBt (68 mg). The reaction mixture was stirred at room temperature for 11 h. The reaction mixture was washed with 1 N aqueous NaOH solution (1.5 mL x 2) and brine (1.5 mL). The organic layer was dried and concentrated. Column chromatography (SiO_2, CH_2Cl_2/MeOH = 95 : 5) afforded 1-(4-chlorobenzyl)-4-[{*N*-(3-ethoxybenzoyl)-D-phenylalanyl}aminomethyl]piperidine (Compound No. **2091**) (183.5 mg, 82%): The purity was determined by RPLC/MS (99%); ESI/MS m/e 534.0 (M^++H, $C_{31}H_{36}ClN_3O_3$).

Examples 1643-1657.

The compounds of this invention were synthesized pursuant to methods of Example 1642 using the corresponding reactant respectively. The ESI/MS data and yields are summarized in Table 32.

Table 32

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 1643	2092	C33 H37 Cl N4 O3	572.8	152.9	64
Example 1644	2093	C27 H36 Cl N3 O3 S	518.0	177.4	82
Example 1645	2094	C29 H34 Cl N3 O3 S	539.9	164.4	73
Example 1646	2095	C28 H38 Cl N3 O3	500.0	139.1	66
Example 1647	2096	C31 H42 Cl N3 O3	540.0	161.7	71
Example 1648	2097	C27 H36 Cl N3 O3	485.8	157.8	78
Example 1649	2098	C31 H35 Cl2 N3 O3	567.9	172.2	72
Example 1650	2099	C30 H34 Cl N3 O3	519.8	144.7	66
Example 1651	2100	C32 H38 Cl N3 O4	564.0	181.5	77
Example 1652	2101	C38 H42 Cl N3 O4	639.9	192.3	72
Example 1653	2103	C33 H40 Cl N3 O4	577.8	159.9	66
Example 1654	2104	C28 H36 Cl N3 O5	530.1	99.7	45
Example 1655	2115	C27 H36 Cl N3 O3	486.2	122.9	60
Example 1656	2116	C28 H38 Cl N3 O3	500.1	118.3	57
Example 1657	2117	C28 H34 Cl N5 O3	524.1	98.3	45

Reference Example 29: Preparation of 1-(*tert*-Butoxycarbonyl)-4-[{*N*-

(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine.

N-{3-(Trifluoromethyl)benzoyl}glycine (4.22 g, 17.0 mmol), EDCI (4.25 g, 22.1 mmol), 1-hydroxybenzotriazole hydrate (2.99 g, 22.1 mmol) and Et_3N (1.72 g) were added to a solution of 1-(*tert*-butoxycarbonyl)-4-(aminomethyl)piperidine (4.03 g) in dry CH_2Cl_2 (200 mL). The reaction mixture was stirred at 25 °C for 20 h. H_2O (100 mL) was added to the reaction mixture and the mixture was extracted with CH_2Cl_2 (2 x 50 mL). The combined extracts were washed with H_2O (2 x 50 mL), brine (50 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to afford an yellow oil which was purified by column chromatography (SiO_2, 70% EtOAc-hexane) to give 1-(*tert*-butoxycarbonyl)-4-[{*N*-(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine as a white solid (6.39 g, 85%): ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.4 (s, 9 H), 1.0-1.8 (m, 5 H), 2.6-2.8 (m, 2 H), 3.15-3.3 (m, 2 H), 4.0-4.3 (m, 4 H), 6.6-6.7 (m, 1H), 7.64 (s, 1 H), 7.60 (dd, 1 H, J = 7.2, 7,2 Hz), 7.79 (d, 1 H, J = 7,2 Hz), 8.0 (d, 1 H, J = 7.2 Hz), 8.11 (s, 1 H); The purity was determined by RPLC/MS (97%); ESI/MS m/e 444.3 (M^++H, $C_{21}H_{28}F_3N_3O_4$).

Reference Example 30: Preparation of 4-[{*N*-(3-(Trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine.

A solution of 1-(*tert*-butoxycarbonyl)-4-[{*N*- (3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine (2.29 g, 5.16 mmol) in CH_3OH (40 mL) was treated with 1 N HCl-Et_2O (55 mL). The reaction mixture was stirred at 25 °C for 15 h and the solvent was removed under reduced pressure. 2 N aqueous NaOH solution (100 mL) was added to the reaction mixture and the mixture was extracted with EtOAc (3 x 100 mL). The combined extracts were washed with brine and dried (K_2CO_3). The solvent was removed under reduced pressure to afford a white solid which was purified by column chromatography (SiO_2, $CH_3OH/CH_2Cl_2/Et_3N$ = 7/6/1)) to give 4-[{*N*-(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine as a white solid (1.27 g, 72%): The purity was determined by RPLC/MS (98%); ESI/MS m/e 344.1 (M^++H, $C_{16}H_{20}F_3N_3O_2$).

Example 1658: Preparation of 1-{3-(Trifluoromethoxy)benzyl}-4-[{*N*-(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine (Compound No. 927).

A solution of 4-[{*N*-(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine (19.9 mg, 0.058 mmol) in CH_3CN (1.0 mL) and (piperidinomethyl)polystyrene (55 mg, 2.7 mmol base/g resin)

were added to a solution of 3-(trifluoromethoxy)benzyl bromide (12.3 mg, 0.048 mmol) in CH_3CN (1.0 mL). The reaction mixture was stirred at 60 °C for 2.5 h. Phenyl isocyanate (6.9 mg, 0.048 mmol) was added to the cooled reaction mixture and the mixture was stirred at 25 °C for 1 h. The reaction mixture was loaded onto Varian™ SCX column and washed with CH_3OH (20 mL). Product was eluted off using 2 N NH_3 in CH_3OH (6 mL) and concentrated to afford 1-{3-(trifluoromethoxy)benzyl}-4-[{*N*-(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine (compound No. **927**) (22.8 mg, 91%) as a pale yellow oil: The purity was determined by RPLC/MS (99%); ESI/MS m/e 518.1 (M^{+}+H, $C_{24}H_{25}F_6N_3O_3$).

Examples 1659-1710.

The compounds of this invention were synthesized pursuant to methods of Example 1658 using the corresponding reactant respectively. The ESI/MS data and yields are summarized in Table 33.

Table 33

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 1659	875	C23 H26 F3 N3 O2	434	6.3	40
Example 1660	876	C23 H25 Br F3 N3 O2	512	4.3	23
Example 1661	877	C24 H25 F3 N4 O2	459	11.3	68
Example 1662	878	C23 H25 F3 N4 O4	479	8.3	48
Example 1663	884	C25 H29 F3 N4 O3	491	10.8	61
Example 1664	885	C24 H28 F3 N3 O4 S	512	9.0	49
Example 1665	886	C23 H25 F4 N3 O2	452	12.7	78
Example 1666	887	C24 H25 F6 N3 O2	502	13.9	77
Example 1667	888	C23 H26 F3 N3 O3	450	11.5	71
Example 1668	889	C29 H30 F3 N3 O2	510	12.4	68
Example 1669	890	C27 H28 F3 N3 O2	484	12.0	69
Example 1670	891	C23 H24 Cl2 F3 N3 O2	502	11.4	63
Example 1671	892	C24 H28 F3 N3 O3	464	11.7	70
Example 1672	893	C24 H26 F3 N5 O5	522	13.9	74
Example 1673	894	C26 H32 F3 N3 O3	492	11.3	64
Example 1674	895	C24 H28 F3 N3 O2	448	4.8	30
Example 1675	896	C24 H25 F3 N4 O2	459	17.5	quant
Example 1676	897	C24 H26 F3 N3 O4	478	9.2	57
Example 1677	898	C24 H26 F3 N3 O4	478	8.9	55

Example 1678	899	C24 H28 F3 N3 O3	464	13.7	82
Example 1679	900	C25 H28 F3 N3 O4	492	18.6	quant
Example 1680	901	C29 H30 F3 N3 O2	510	13.7	75
Example 1681	902	C23 H24 F3 N5 O6	524	12.6	67
Example 1682	903	C25 H30 F3 N3 O4	494	14.0	79
Example 1683	906	C25 H30 F3 N3 O2	462	11.2	67
Example 1684	907	C31 H34 F3 N3 O2	538	19.6	75
Example 1685	908	C30 H31 F3 N4 O3	553	30.4	76
Example 1686	909	C30 H31 F3 N4 O3	553	12.6	63
Example 1687	910	C23 H24 Cl2 F3 N3 O2	502	11.0	61
Example 1688	911	C23 H25 Cl F3 N3 O2	468	20.2	89
Example 1689	912	C23 H24 Br2 F3 N3 O2	590	20.2	95
Example 1690	913	C24 H28 F3 N3 O3	464	12.6	76
Example 1691	914	C30 H32 F3 N3 O3	540	13.9	72
Example 1692	915	C24 H28 F3 N3 O3	464	8.3	25
Example 1693	916	C22 H25 F3 N4 O2	435	2.5	8
Example 1694	917	C22 H25 F3 N4 O2	435	2.7	9
Example 1695	918	C26 H30 F3 N3 O4	506	3.9	22
Example 1696	919	C24 H28 F3 N3 O2	448	15.9	99
Example 1697	920	C24 H25 F6 N3 O3	518	20.3	81
Example 1698	921	C27 H28 F3 N3 O2	484	15.5	89
Example 1699	922	C20 H26 F3 N3 O2	398	7.3	51
Example 1700	923	C29 H29 Cl F3 N3 O2	544	12.5	48
Example 1701	928	C24 H25 F6 N3 O3	518	21.4	86
Example 1702	929	C24 H28 F3 N3 O2 S	480	23.7	quant
Example 1703	930	C24 H28 F3 N3 O2	448	21.3	99
Example 1704	931	C24 H25 F3 N4 O2	459	21.4	97
Example 1705	932	C23 H24 Cl F3 N4 O4	513	15.6	63
Example 1706	933	C24 H28 F3 N3 O2	448	16.6	77
Example 1707	934	C22 H25 F3 N4 O2	435	18.0	43
Example 1708	935	C23 H25 F3 N4 O4	479	15.1	65
Example 1709	936	C23 H25 F3 N4 O4	479	15.4	67
Example 1710	1615	C24 H25 F6 N3 O2 S	534.2	26.3	99

Example 1711: Preparation of 1-{4-(Dimethylamino)benzyl}-4-[{*N*-(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine (Compound No. 937).

A solution of 4-[{*N*-(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine (20.0 mg, 0.058 mmol) in CH_3OH (1.0 mL) and $NaBH_3CN$ (16.5 mg) were added to a solution of 4-

(dimethylamino)benzaldehyde (30.4 mg, 0.204 mmol) in 5 % CH_3COOH/CH_3OH (1.0 mL). The reaction mixture was stirred at 60 °C for 19 h. The solvent was evaporated to afford a solid. CH_3CN (2.0 mL) and phenyl isocyanate (6.9 mg, 0.048 mmol) were added to the solid and the mixture was stirred at 25 °C for 1 h. The reaction mixture was loaded onto Varian™ SCX column and washed with CH_3OH (20 mL). Product was eluted using 2 N NH_3-CH_3OH (6 mL) and the eluant was concentrated to afford 1-(4-(dimethylamino)benzyl)-4-[{*N*-(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine (compound No. **937**) as a pale yellow oil (13.5 mg, 49%): The purity was determined by RPLC/MS (87%); ESI/MS m/e 477.3 (M^++H, $C_{25}H_{31}F_3N_4O_2$).

Examples 1712-1729.

The compounds of this invention were synthesized pursuant to methods of Example 1711 using the corresponding reactant respectively. Preparative TLC (SiO_2), if needed, afforded the desired material. The ESI/MS data and yields are summarized in Table 34.

Table 34

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 1712	879	C24 H26 F3 N3 O4	478	13.0	62
Example 1713	880	C24 H26 F3 N3 O4	478	16.3	78
Example 1714	881	C23 H25 Br F3 N3 O2	512	11.4	51
Example 1715	882	C29 H30 F3 N3 O3	526	13.4	58
Example 1716	883	C23 H25 Cl F3 N3 O2	468	7.9	39
Example 1717	904	C23 H26 F3 N3 O3	450	3.3	17
Example 1718	905	C21 H23 F3 N4 O4 S	485	27.7	98
Example 1719	938	C23 H24 Cl F4 N3 O2	486	8.6	30
Example 1720	939	C23 H24 Cl F3 N4 O4	513	11.0	37
Example 1721	940	C23 H26 F3 N3 O3	450	5.5	21
Example 1722	941	C24 H24 Cl F6 N3 O2	536	11.2	36
Example 1723	987	C30 H32 F3 N3 O2	524	17.5	76
Example 1724	1449	C25 H30 F3 N3 O2	462	21.6	80
Example 1725	1450	C26 H32 F3 N3 O2	476	23.5	85
Example 1726	1452	C27 H35 F3 N4 O2	505	5.1	17
Example 1727	1453	C26 H32 F3 N3 O3	492	22.0	77
Example 1728	1454	C25 H30 F3 N3 O3	478	21.4	77
Example 1729	1456	C25 H28 F3 N3 O4	492	23.8	83

Example 1730: Preparation of 1-{3-Hydroxy-4-methoxybenzyl}-4-[{*N*-(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine (Compound No. 1452).

To a solution of 4-[{*N*-(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine (20.0 mg, 0.058 mmol) and 3-hydroxy-4-methoxybenzaldehyde (33 mg) in 5 % CH_3COOH/CH_3OH (1.0 mL) was added $NaBH_3CN$ (16.5 mg) in 5 % CH_3COOH/CH_3OH (1.0 mL). The reaction mixture was stirred at 60 °C for 15 h. The reaction mixture was loaded onto Varian™ SCX column and washed with CH_3OH (15 mL). Product was eluted using 2 N NH_3-CH_3OH (5 mL) and the eluant was concentrated to afford 1-{3-hydroxy-4-methoxybenzyl}-4-[{*N*-(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine (Compound No. **1452**) (25.8 mg, 92%): The purity was determined by RPLC/MS (91%); ESI/MS m/e 480 (M^++H, $C_{24}H_{28}F_3N_3O_4$).

Examples 1731-1733.

The compounds of this invention were synthesized pursuant to methods of Example 1730 using the corresponding reactant respectively. The ESI/MS data and yields are summarized in Table 35.

Table 35

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 1731	1455	C24 H28 F3 N3 O4	480	24.0	86
Example 1732	1647	C27 H34 F3 N3 O2	490.2	23.6	96
Example 1733	1649	C26 H32 F3 N3 O2	476.2	23.1	97

Example 1734: Preparation of 1-(4-Benzylbenzyl)-4-[{*N*-(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine (Compound No. 926).

A solution of methanesulfonyl chloride (4.2 mg, 0.037 mmol) in $CHCl_3$ (1.0 mL) and (piperidinomethyl)polystyrene (54 mg, 2.7 mmol base/g resin) were added to a solution of 4-(benzyl)benzyl alcohol (8.7 mg, 0.044 mmol) in $CHCl_3$ (1.0 mL). The reaction mixture was stirred at 25 °C for 15 h. A solution of 4-[{*N*-(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine (15.1 mg, 0.044 mmol) in CH_3CN (1.0 mL) and KI (2 mg) were added to the reaction mixture and the mixture was stirred at 65 °C for 5 h. Phenyl isocyanate (5.2 mg) was added to the cooled reaction mixture and the mixture was stirred at 25 °C for 1 h. The reaction mixture was loaded onto Varian™ SCX column and washed with CH_3OH

(20 mL). Product was eluted off using 2 N NH_3 in CH_3OH (6 mL) and concentrated to afford 1-(4-benzylbenzyl)-4-[{*N*-(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine (compound No. **926**) as a pale yellow oil (5.6 mg, 29%): The purity was determined by RPLC/MS (94%); ESI/MS m/e 524.1 (M^++H, $C_{30}H_{32}F_3N_3O_2$).

Reference Example 31: Preparation of 4-[{(*N*-(Benzyloxycarbonyl)glycyl)amino}methyl]-1-(*tert*-butoxycarbonyl)piperidine.

A solution of 4-(aminomethyl)-1-(*tert*-butoxycarbonyl)piperidine (3.54 g, 16.5 mmol) in CH_2Cl_2 (80 mL) was treated with Et_3N (2.8 mL, 20 mmol), *N*-(benzyloxycarbonyl)glycine (3.77 g, 18 mmol), EDCI (3.45 g, 18 mmol) and HOBt (2.43 g, 18 mmol). After the reaction mixture was stirred at room temperature for 15 h, 2 N aqueous NaOH solution (100 mL) was added. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (100 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography (SiO_2, ethyl acetate) afforded the desired 4-[{(*N*-(Benzyloxycarbonyl)glycyl)amino}methyl]-1-(*tert*-butoxycarbonyl)piperidine (6.27 g, 94%) as an amorphous solid.

Reference Example 32: Preparation of 4-{(Glycylamino}methyl}-1-(*tert*-butoxycarbonyl)piperidine.

A solution of 4-[{(*N*-(benzyloxycarbonyl)glycyl)amino}methyl]-1-(*tert*-butoxycarbonyl)piperidine (6.26 g, 15.4 mmol) in methanol (100 mL) was hydrogenated at 1 atm in the presence of 5% palladium on charcoal (620 mg) at room temperature for 7 h. The catalyst was removed by filtration through Celite and the combined filtrate was concentrated to afford 4-{(glycylamino}methyl}-1-(*tert*-butoxycarbonyl)piperidine (3.84 g, 92%) as a solid.

Reference Example 33: Preparation of 4-[{(*N*-(2-Amino-5-chlorobenzoyl)glycyl)amino}methyl]-1-(*tert*-butoxycarbonyl)piperidine.

A solution of 4-{(glycylamino}methyl}-1-(*tert*-butoxycarbonyl)piperidine (1.33 g, 4.90 mmol) in CH_2Cl_2 (25 mL) was treated with Et_3N (0.75 mL, 5.4 mmol), 2-amino-5-chlorobenzoic acid (840 mg, 4.9 mmol), EDCI (940 mg, 4.9 mmol) and HOBt (660 mg, 4.9 mmol). After the reaction mixture was stirred at room temperature for 3 h, 2 N aqueous NaOH solution (20 mL) was added. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (20 mL x 3). The combined organic layers were dried over

anhydrous sodium sulfate, filtered, and concentrated. Column chromatography (SiO_2, ethyl acetate) afforded the desired 4-[{(*N*-(2-amino-5-chlorobenzoyl)glycyl)amino}methyl]-1-(*tert*-butoxycarbonyl)piperidine (1.63 g, 78%) as a solid.

Reference Example 34: Preparation of 4-[{(N-(2-Amino-5-chlorobenzoyl)glycyl)amino}methyl]piperidine.

To a solution of 4-[{(*N*-(2-amino-5-chlorobenzoyl)glycyl)amino}methyl]-1-(*tert*-butoxycarbonyl)piperidine (1.63 g, 3.84 mmol) in methanol (20 mL) was added 4 N HCl in dioxane (9.5 mL). The solution was stirred at room temperature for 6 h. The reaction mixture was concentrated and 2 N aqueous NaOH solution (20 mL) was added. The mixture was extracted with dichloromethane (20 mL x 3), and the combined extracts were dried over sodium sulfate, filtered and concentrated to give 4-[{(*N*-(2-amino-5-chlorobenzoyl)glycyl)amino}methyl]piperidine (1.19 g, 95%): ^1H NMR ($CDCl_3$, 270 MHz) δ 1.10-1.76 (m, 4 H), 2.55 (td, J = 2.4 and 12.2 Hz, 2 H), 3.00-3.10 (m, 2 H), 3.17 (t, J = 6.2 Hz, 2 H), 3.48 (s, 2 H), 4.03 (d, J = 4.9 Hz, 2 H), 5.50 (br. s, 2 H), 6.11-6.23 (m, 1 H), 6.60 (d, J = 8.8 Hz, 1 H), 6.85-7.02 (m, 1 H), 7.15 (dd, J = 2.7 and 8.8 Hz, 1 H), 7.38 (d, J = 2.4 Hz, 1 H); ESI/MS m/e 325.2 ($C_{15}H_{21}ClN_4O_2$).

4-[{(*N*-(2-Amino-5-bromobenzoyl)glycyl)amino}methyl]piperidine was also synthesized pursuant to methods of Reference Examples 32 and 33 using the corresponding reactant: 951 mg, 64% (2 steps).ESI/MS m/e 369.2 ($C_{15}H_{21}BN_4O_2$).

Example 1735: Preparation of 4-[{(N-(2-(*tert*-Butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl)amino}methyl]-1-(4-chlorobenzyl)piperidine.

A solution of 1-(4-chlorobenzyl)-4-{(glycylamino)methyl}piperidine dihydrochloride (738 mg, 2 mmol) in CH_2Cl_2 (20 mL) was treated with Et_3N (1.1 mL, 8 mmol), 2-(*tert*-butoxycarbonylamino)-4,5-difluorobenzoic acid (607 mg, 2.2 mmol), EDCI (422 mg, 2.2 mmol) and HOBt (337 mg, 2.2 mmol). After the reaction mixture was stirred at room temperature for 14 h, 0.6 N aqueous NaOH solution (50 mL) was added, and the mixture was extracted with dichloromethane (3 times). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography (SiO_2, ethyl acetate then ethyl acetate/methanol = 92/8) afforded the desired 4-[{(*N*-(2-(*tert*-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl)amino}methyl]-1-(4-chlorobenzyl)piperidine (1.01 g, 92%): ESI/MS m/e 551.3 (M^++H, $C_{27}H_{33}ClF_2N_4O_4$).

4-[{(*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl)amino}methyl]-1-(4-chlorobenzyl)piperidine was also prepared pursuant to the above method using the corresponding reactant: 3.03 g, 82%; ESI/MS m/e 583.2 (M^{+}+H, $C_{28}H_{34}ClF_3N_4O_4$).

Reference Example 35: Preparation of 4-[{(N-(2-Amino-5-trifluoromethylbenzoyl)glycyl)amino}methyl]piperidine.

A suspension of 1-(4-chlorobenzyl)-4-[{(N-(2-amino-5-trifluoromethylbenzoyl)glycyl)amino}methyl]piperidine (447 mg, 0.93 mmol) and $Pd(OH)_2$ (60 mg, 0.23 mmol) in 5% HCO_2H/methanol (10 mL) was stirred at 50 °C for 14 h. The Pd catalyst was filtered off through Celite, and the filtrate was concentrated. To the residue was added 1N aqueous NaOH solution (15 mL) and the mixture was extracted with ethyl acetate (30 mL x 3). The combined extracts were dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography (SiO_2, AcOEt/MeOH/Et_3N = 70/25/5) gave 4-[{(N-(2-amino-5-trifluoromethylbenzoyl)glycyl)amino}methyl]piperidine (284 mg, 86%): ESI/MS m/e 359.0 (M^{+}+H, $C_{16}H_{21}F_3N_4O_2$).

4-[{(N-(2-Amino-4,5-difluorobenzoyl)glycyl)amino}methyl]piperidine, 4-[{N-(2-(*tert*-Butoxycarbonylamino)-5-trifluoromethoxybenzoyl)glycyl}aminomethyl]piperidine, 4-[{(*N*-(2-(*tert*-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl)amino}methyl]piperidine, and 4-[{(*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl)amino}methyl]piperidine were also prepared pursuant to the above method using the corresponding reactant, respectively.

4-[{(N-(2-amino-4,5-difluorobenzoyl)glycyl)amino}methyl]piperidine: 564 mg, 89%; ESI/MS m/e 327.2 (M^{+}+H, $C_{15}H_{20}F_2N_4O_2$).

4-[{N-(2-(*tert*-Butoxycarbonylamino)-5-trifluoromethoxybenzoyl)glycyl}aminomethyl]piperidine: quant; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.10-1.25 (m, 2 H), 1.45-1.73 (m, 3 H), 1.51 (s, 9 H), 2.53-2.64 (m, 2 H), 3.04-3.13 (m, 2 H), 3.22 (t, J = 6.3 Hz, 2 H), 4.09 (d, J = 4.6 Hz, 2 H), 5.91 (br. s, 1 H), 7.08 (br. s., 1 H), 7.32 (d, J = 9.0 Hz, 1 H), 7.38 (s, 1 H), 8.43 (d, J = 9.0 Hz, 1 H).

4-[{(*N*-(2-(*tert*-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl)amino}methyl]piperidine: 310 mg, 40%; ESI/MS m/e 427.3 (M^{+}+H, $C_{20}H_{28}F_2N_4O_4$).

4-[{(*N*-(2-(*tert*-butoxycarbonylamino)-5-

trifluoromethylbenzoyl)glycyl)amino}methyl]piperidine: 1.35 g, 57%; ESI/MS m/e 459.3 (M^{+}+H, $C_{21}H_{29}F_3N_4O_4$).

Example 1736: Preparation of 4-[{*N*-(2-Amino-5-chlorobenzoyl)glycyl}aminomethyl]-1-(4-ethoxybenzyl)piperidine (Compound No. 1429) and 1-(4-Ethoxybenzyl)-4-[{*N*-(2-(4-ethoxybenzyl)amino-5-chlorobenzoyl)glycyl}aminomethyl]piperidine (Compound No. 1433).

Sodium cyanoborohydride (140 mmol) in methanol (0.4 mL) was added to a mixture of 4-[{*N*-(2-amino-5-chlorobenzoyl)glycyl}aminomethyl]piperidine (0.10 mmol), 4-ethoxybenzaldehyde (0.10 mmol), acetic acid (0.050 mL), and methanol (1.6 mL). The reaction mixture was stirred at 60 °C for 14 h. The reaction mixture was loaded onto Varian™ SCX column and washed with CH_3OH (20 mL). Product was eluted using 2 N NH_3 in CH_3OH (6 mL) and concentrated. Preparative TLC (SiO2, AcOEt/CH3OH 5 : 1) afforded 4-[{*N*-(2-amino-5-chlorobenzoyl)glycyl}aminomethyl]-1-(4-ethoxybenzyl)piperidine (Compound No. **1429**) and 1-(4-ethoxybenzyl)-4-[{*N*-(2-(4-ethoxybenzyl)amino-5-chlorobenzoyl)glycyl}aminomethyl]piperidine (Compound No. **1433**).

Compound No. **1429**: 4.5 mg, 20%: The purity was determined by RPLC/MS (95%); ESI/MS m/e 459.2 (M^{+}+H, $C_{24}H_{31}ClN_4O_3$).

Compound No. **1433**: 8.4 mg, 28%: The purity was determined by RPLC/MS (98%); ESI/MS m/e 593.2 (M^{+}+H, $C_{33}H_{41}ClN_4O_4$).

Examples 1737-1779.

The compounds of this invention were synthesized pursuant to methods of Example 1736 using the corresponding reactant respectively. The ESI/MS data and yields are summarized in Table 36.

Table 36

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 1737	1430	C24 H29 Cl N4 O4	473.0	3.1	13
Example 1738	1431	C24 H31 Br N4 O3	505.2	5.8	23
Example 1739	1432	C24 H29 Br N4 O4	517.0	4.1	16
Example 1740	1434	C33 H41 Br N4 O6	637.2	9.7	30
Example 1741	1435	C24 H31 Cl N4 O2	443.2	9.7	44
Example 1742	1436	C25 H33 Cl N4 O2	457.2	12.5	55
Example 1743	1437	C25 H33 Cl N4 O3	473.2	9.4	40

Example 1744	1438	C24 H31 Br N4 O2	489.2	5.9	24
Example 1745	1439	C25 H33 Br N4 O2	503.2	15.2	61
Example 1746	1440	C25 H33 Br N4 O3	519.2	11.0	43
Example 1747	1441	C23 H29 Br N4 O2 S	507.2	9.3	37
Example 1748	1442	C33 H41 Cl N4 O2	561.4	6.8	24
Example 1749	1443	C35 H45 Cl N4 O2	589.4	9.8	33
Example 1750	1444	C35 H45 Cl N4 O4	621.4	9.4	30
Example 1751	1445	C33 H41 Br N4 O2	605.2	6.5	21
Example 1752	1446	C35 H45 Br N4 O2	635.2	10.7	34
Example 1753	1447	C35 H45 Br N4 O4	665.4	12.4	37
Example 1754	1448	C31 H37 Br N4 O2 S2	643.2	7.6	24
Example 1755	1457	C24 H32 Cl N5 O2	458.2	4.5	20
Example 1756	1458	C23 H29 Cl N4 O4	461.2	6.0	26
Example 1757	1459	C24 H32 Br N5 O2	504.0	6.8	27
Example 1758	1460	C23 H29 Br N4 O4	505.0	8.0	32
Example 1759	1461	C31 H37 Cl N4 O6	597.2	5.9	20
Example 1760	1462	C31 H37 Br N4 O6	643.2	6.0	19
Example 1761	1514	C26 H36 Cl N5 O2	486.2	5.5	23
Example 1762	1515	C23 H29 Cl N4 O4	463.0	5.8	25
Example 1763	1516	C26 H36 Br N5 O2	530.2	4.2	16
Example 1764	1517	C23 H29 Br N4 O4	505.0	6.5	26
Example 1765	1518	C31 H37 Cl N4 O6	597.2	4.3	14
Example 1766	1519	C31 H37 Br N4 O6	641.2	5.3	17
Example 1767	1570	C23 H29 Cl N4 O2 S	461.0	2.7	12
Example 1768	1571	C31 H37 Cl N4 O2 S2	597.2	4.9	16
Example 1769	1651	C37 H49 Br N4 O2	663.2	5.5	17
Example 1770	1652	C26 H35 Br N4 O2	515.2	6.0	23
Example 1771	1653	C35 H45 Br N4 O2	633.2	5.0	16
Example 1772	1654	C25 H33 Br N4 O2	501.0	6.2	25
Example 1773	1655	C37 H49 Cl N4 O2	617.4	5.6	18
Example 1774	1656	C26 H35 Cl N4 O2	471.2	5.9	25
Example 1775	1657	C35 H45 Cl N4 O2	589.2	4.6	16
Example 1776	1658	C25 H33 Cl N4 O2	457.2	5.3	23
Example 1777	1785	C26 H33 F3 N4 O2	491.2	4.7	12.8
Example 1778	1786	C25 H29 F3 N4 O3	491.2	3.7	10.1
Example 1779	1804	C25 H32 F2 N4 O2	459.2	3.3	9.6

Example 1780: Preparation of 4-[{*N*-(2-Amino-5-trifluoromethoxybenzoyl)glycyl}aminomethyl]-1-(4-isopropylbenzyl)piperidine

(Compound No. 1903).

To a mixture of 4-[{*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethoxy)benzoylglycyl}aminomethyl]piperidine (0.050 mmol), 4-isopropylbenzaldehyde (0.060 mmol), $NaBH_3CN$ (0.15 mmol), and methanol (1.3 mL) was added acetic acid (0.050 mL). The reaction mixture was stirred at 60 °C for 8 h. The mixture was cooled to room temperature, loaded onto Varian™ SCX column, and washed with CH_3OH (10 mL). Product was eluted off using 2 N NH_3 in CH_3OH (5 mL) and concentrated. To the resulting material was added 4 N HCl in 1,4-dioxane (2 mL) and the solution was stirred overnight at room temperature. Concentration and preparative TLC gave 4-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}aminomethyl]-1-(4-isopropylbenzyl)piperidine (Compound No. **1903**) (6.6 mg, 26%): The purity was determined by RPLC/MS (93%); ESI/MS m/e 507 (M^++H, $C_{26}H_{33}F_3N_4O_3$).

Examples 1781-1783.

The compounds of this invention were synthesized pursuant to methods of Example 1780 using the corresponding reactant respectively. The ESI/MS data and yields are summarized in Table 37.

Table 37

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 1781	1904	C26 H33 F3 N4 O3	507	9.6	37.9
Example 1782	1917	C25 H31 F3 N4 O5	525.2	1.2	3.1
Example 1783	1918	C24 H29 F3 N4 O4	495.2	2.8	7.5

Example 1784: Preparation of 4-[{*N*-(2-Amino-4,5-difluorobenzoyl)glycyl}aminomethyl]-1-(5-bromo-2-ethoxybenzyl)piperidine (Compound No. 2052).

To a mixture of 4-[{*N*-(2-(*tert*-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl}aminomethyl]piperidine (0.050 mmol), 5-bromo-2-ethoxybenzaldehyde (0.15 mmol), methanol (1.2 mL), and acetic acid (0.030 mL) was added $NaBH_3CN$ (0.25 mmol) in methanol (0.50 mL). The reaction mixture was stirred at 50 °C for 13 h. The mixture was cooled to room temperature, loaded onto Varian™ SCX column, and washed with CH_3OH (5 mL x 3). Product was eluted off using 2 N NH_3 in CH_3OH (5 mL) and concentrated. To the resulting material were added dichloromethane (1 mL) and trifluoroacetic acid (TFA) (0.50 mL) and

the solution was stirred at room temperature for 10 min. The reaction mixture was concentrated, and the residue was dissolved in methanol, loaded onto Varian™ SCX column, and washed with CH_3OH (5 mL x 2). Product was eluted off using 2 N NH_3 in CH_3OH (5 mL) and concentrated. Preparative TLC (SiO2, ethyl acetate/methanol = 10/1) gave 4-[{*N*-(2-amino-4,5-difluorobenzoyl)glycyl}aminomethyl]-1-(5-bromo-2-ethoxybenzyl)piperidine (Compound No. **2052**) (10.2 mg, 38%): The purity was determined by RPLC/MS (96%); ESI/MS m/e 539.2 (M^++H, $C_{24}H_{29}BrF_2N_4O_3$).

Examples 1785-1792.

The compounds of this invention were synthesized pursuant to methods of Example 1784 using the corresponding reactant respectively. The ESI/MS data and yields are summarized in Table 38.

Table 38

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 1785	2053	C30 H34 F2 N4 O4	553.4	12.7	46
Example 1786	2054	C27 H30 F2 N4 O3	497.2	13.7	55
Example 1787	2055	C23 H28 F2 N4 O4	463.2	10.1	44
Example 1788	2056	C22 H24 Br F3 N4 O2	515.2	7.7	30
Example 1789	2057	C23 H27 Br F2 N4 O3	527.0	8.6	33
Example 1790	2058	C24 H30 F2 N4 O4	477.2	6.4	27
Example 1791	2059	C28 H30 F2 N4 O3	509.4	6.7	26
Example 1792	2060	C25 H32 F2 N4 O5	507.2	7.2	28

Example 1793: Preparation of 4-[{*N*-(2-Amino-4,5-difluorobenzoyl)glycyl}aminomethyl]-1-(3,4-diethoxybenzyl)piperidine (Compound No. 2065).

To a mixture of 4-[{*N*-(2-(*tert*-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl}aminomethyl]piperidine (0.050 mmol), 3,4-diethoxybenzaldehyde (0.15 mmol), methanol (1.2 mL), and acetic acid (0.050 mL) was added $NaBH_3CN$ (0.25 mmol) in methanol (0.50 mL). The reaction mixture was stirred at 50 °C overnight. The mixture was cooled to room temperature, loaded onto Varian™ SCX column, and washed with CH_3OH (5 mL x 2). Product was eluted off using 2 N NH_3 in CH_3OH (5 mL) and concentrated. To the resulting material were added dichloromethane (2 mL) and phenyl isocyanate (0.10 mL) and the solution was stirred at room temperature for 1 h, loaded onto Varian™ SCX column, and

washed with CH_3OH (5 mL x 2). Product was eluted off using 2 N NH_3 in CH_3OH (5 mL) and concentrated. The residue was dissolved in methanol (0.25 mL) and 4 N HCl in dioxane (0.125 mL) was added. The solution was stirred at room temperature overnight and concentrated. The residue was dissolved in methanol, loaded onto Varian™ SCX column, and washed with CH_3OH (5 mL x 2). Product was eluted off using 2 N NH_3 in CH_3OH (5 mL) and concentrated to afford 4-[{*N*-(2-amino-4,5-difluorobenzoyl)glycyl}aminomethyl]-1-(3,4-diethoxybenzyl)piperidine (Compound No. **2065**) (21.2 mg, 84%): The purity was determined by RPLC/MS (97%); ESI/MS m/e 505.2 (M^++H, $C_{26}H_{34}F_2N_4O_4$).

Examples 1794-1808.

The compounds of this invention were synthesized pursuant to methods of Example 1793 using the corresponding reactant respectively. The ESI/MS data and yields are summarized in Table 39.

Table 39

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 1794	2061	C23 H27 F3 N4 O2	449.2	12.6	56
Example 1795	2062	C23 H27 F3 N4 O3	465.2	19.7	85
Example 1796	2063	C25 H32 F2 N4 O4	491.2	19.8	81
Example 1797	2064	C22 H24 Br F3 N4 O2	515.2	17.5	68
Example 1798	2066	C29 H32 F2 N4 O3	523.2	18.0	69
Example 1799	2067	C26 H34 F2 N4 O2	473.2	21.9	93
Example 1800	2068	C22 H24 Cl F3 N4 O2	469.2	11.2	48
Example 1801	2069	C24 H30 F2 N4 O3	461.4	20.2	88
Example 1802	2070	C23 H27 Br F2 N4 O3	527.2	17.7	67
Example 1803	2071	C24 H30 F2 N4 O4	477.2	10.9	46
Example 1804	2072	C25 H32 F2 N4 O3	475.2	19.3	81
Example 1805	2073	C29 H32 F2 N4 O3	523.2	22.8	87
Example 1806	2074	C29 H32 F2 N4 O4	539.2	22.5	84
Example 1807	2075	C23 H27 F3 N4 O3	465.2	14.9	64
Example 1808	2076	C22 H24 F4 N4 O2	453.2	21.9	97

Example 1809: Preparation of 4-[{*N*-(2-Amino-4,5-difluorobenzoyl)glycyl}aminomethyl]-1-(2-hydroxy-3-methylbenzyl)piperidine (Compound No. 2106).

To a mixture of 4-[{*N*-(2-(*tert*-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl}aminomethyl]piperidine (0.050 mmol), 2-hydroxy-3-

methylbenzaldehyde (0.25 mmol), methanol (1.0 mL), and acetic acid (0.040 mL) was added $NaBH_3CN$ (0.40 mmol) in methanol (0.50 mL). The reaction mixture was stirred at 50 °C overnight. The mixture was cooled to room temperature, loaded onto Varian™ SCX column, and washed with CH_3OH (5 mL x 2). Product was eluted off using 2 N NH_3 in CH_3OH (5 mL) and concentrated. The resulting material was dissolved into ethyl acetate/methanol = 5:1 (1 mL), loaded onto Varian™ Si column, eluted off using ethyl acetate/methanol = 5:1 (5 mL), and concentrated. The residue was dissolved in methanol (2 mL) and 4 N HCl in dioxane (0.50 mL) was added. The solution was stirred at room temperature overnight and concentrated. The residue was dissolved in methanol, loaded onto Varian™ SCX column, and washed with CH_3OH (5 mL x 2). Product was eluted off using 2 N NH_3 in CH_3OH (5 mL) and concentrated. Preparative TLC afforded 4-[{*N*-(2-amino-4,5-difluorobenzoyl)glycyl}aminomethyl]-1-(2-hydroxy-3-methylbenzyl)piperidine (Compound No. **2106**): The purity was determined by RPLC/MS (97%); ESI/MS m/e 447.0 (M^{+}+H, $C_{23}H_{28}F_2N_4O_3$).

Examples 1810-1823.

The compounds of this invention were synthesized pursuant to methods of Example 1809 using the corresponding reactant respectively. The ESI/MS data and yields are summarized in Table 40.

Table 40

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 1810	2077	C22 H25 Cl F2 N4 O3	467.2	3.7	16
Example 1811	2078	C24 H30 F2 N4 O4	477.2	1.9	8
Example 1812	2079	C30 H34 F2 N4 O4	553.4	4.8	17
Example 1813	2080	C22 H25 Cl F2 N4 O3	467.2	13.5	58
Example 1814	2081	C22 H25 Cl F2 N4 O3	467.2	13.8	59
Example 1815	2082	C23 H28 F2 N4 O4	463.2	9.6	42
Example 1816	2105	C23 H28 F2 N4 O4	463.2	ND	ND
Example 1817	2106	C23 H28 F2 N4 O3	447.0	ND	ND
Example 1818	2107	C20 H23 Br F2 N4 O2 S	503.1	ND	ND
Example 1819	2108	C25 H28 F2 N4 O2 S	487.2	ND	ND
Example 1820	2109	C20 H23 Br F2 N4 O3	487.0	ND	ND
Example 1821	2110	C22 H28 F2 N4 O3	435.1	ND	ND
Example 1822	2111	C22 H24 Cl F3 N4 O2	469.0	ND	ND
Example 1823	2112	C24 H29 Br F2 N4 O4	557.0	ND	ND

ND: Not determined.

Example 1824: Preparation of 4-[{*N*-(2-Amino-4,5-difluorobenzoyl)glycyl}aminomethyl]-1-(3-amino-4-methylbenzyl)piperidine (Compound No. 2114).

To a mixture of 4-[{*N*-(2-(*tert*-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl}aminomethyl]piperidine (0.050 mmol), 4-methyl-3-nitrobenzaldehyde (0.25 mmol), methanol (1.2 mL), and acetic acid (0.050 mL) was added $NaBH_3CN$ (0.50 mmol) in methanol (1.0 mL). The reaction mixture was stirred at 50 °C overnight. The mixture was cooled to room temperature, loaded onto Varian™ SCX column, and washed with CH_3OH (5 mL x 2). Product was eluted off using 2 N NH_3 in CH_3OH (5 mL) and concentrated. The resulting material was dissolved into ethyl acetate/methanol = 2/1 (2 mL), loaded onto Varian™ Si column, eluted off using ethyl acetate/methanol = 2/1 (6 mL), and concentrated. The residue was dissolved in methanol (1 mL) and 4 N HCl in dioxane (0.50 mL) was added. The solution was stirred at room temperature overnight and concentrated. The residue was dissolved in methanol, loaded onto Varian™ SCX column, washed with CH_3OH (5 mL x 2), and eluted off using 2 N NH_3 in CH_3OH (5 mL). Concentration afforded 4-[{*N*-(2-amino-4,5-difluorobenzoyl)glycyl}aminomethyl]-1-(4-methyl-3-nitrobenzyl)piperidine.

A mixture of 4-[{*N*-(2-amino-4,5-difluorobenzoyl)glycyl}aminomethyl]-1-(4-methyl-3-nitrobenzyl)piperidine prepared above, 5% palladium-activated carbon (15 mg), and methanol (2 mL) was stirred under a hydrogen atmosphere at room temperature for 4 h. The Pd catalyst was filtered off through Celite and the filtrate was concentrated. Preparative TLC (SiO_2, ethyl acetate/MeOH = 3/1) gave 4-[{*N*-(2-amino-4,5-difluorobenzoyl)glycyl}aminomethyl]-1-(3-amino-4-methylbenzyl)piperidine (Compound No. **2114**) (2.9 mg, 13%): The purity was determined by RPLC/MS (100%); ESI/MS m/e 446.1 (M^{+}+H, $C_{23}H_{29}F_2N_5O_2$).

Example 1825: Preparation of 4-[{*N*-(2-Amino-4,5-difluorobenzoyl)glycyl}aminomethyl]-1-(3-amino-4-methoxybenzyl)piperidine (Compound No. 2113).

The titled compound, 4-[{*N*-(2-amino-4,5-difluorobenzoyl)glycyl}aminomethyl]-1-(3-amino-4-methoxybenzyl)piperidine (Compound No. **2113**), was synthesized pursuant to methods of Example 1824 using the corresponding reactant: 4.6 mg, 20% yield; ESI/MS m/e 462.2 (M^{+}+H, $C_{23}H_{29}F_2N_5O_3$).

Example 1826: Preparation of 1-(3-Amino-4-hydroxybenzyl)-4-[{*N*-(2-

(*tert*-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl}aminomethyl]piperidine.

To a mixture of 4-[{*N*-(2-(*tert*-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl}aminomethyl]piperidine (0.35 mmol), 4-hydroxy-3-nitrobenzaldehyde (1.22 mmol), methanol (3.8 mL), and acetic acid (0.175 mL) was added $NaBH_3CN$ (1.58 mmol) in methanol (3.2 mL). The reaction mixture was stirred at 50 °C overnight. The mixture was cooled to room temperature, loaded onto Varian™ SCX column, and washed with CH_3OH. Product was eluted off using 2 N NH_3 in CH_3OH and concentrated. The resulting material was dissolved into ethyl acetate/methanol = 5/1, loaded onto Varian™ Si column, eluted off using ethyl acetate/methanol = 5/1 (10 mL), and concentrated to give 4-[{*N*-(2-(*tert*-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl}aminomethyl]-1-(4-hydroxy-3-nitrobenzyl)piperidine (175 mg, 87%).

A mixture of 4-[{*N*-(2-(*tert*-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl}aminomethyl]-1-(4-hydroxy-3-nitrobenzyl)piperidine prepared above, 10% palladium-activated carbon (45 mg), and methanol (5 mL) was stirred under a hydrogen atmosphere at room temperature for 2 h. The Pd catalyst was filtered off and the filtrate was concentrated to afford 1-(3-amino-4-hydroxybenzyl)-4-[{*N*-(2-(*tert*-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl}aminomethyl]piperidine (100 mg, 60%).

Example 1827: Preparation of 4-[{*N*-(2-Amino-4,5-difluorobenzoyl)glycyl}aminomethyl]-1-(3-amino-4-hydroxybenzyl)piperidine (Compound No. 2141).

To a solution of 1-(3-amino-4-hydroxybenzyl)-4-[{*N*-(2-(*tert*-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl}aminomethyl]piperidine (20.0 mg, 0.035 mmol) in methanol (1 mL) was added 4 N HCl in dioxane (0.50 mL) and the solution was stirred at room temperature overnight. After the solution was concentrated, the residue was dissolved in methanol, loaded onto Varian™ SCX column, washed with CH_3OH (5 mL x 2), and eluted off using 2 N NH_3 in CH_3OH (5 mL). Concentration afforded 4-[{*N*-(2-amino-4,5-difluorobenzoyl)glycyl}aminomethyl]-1-(3-amino-4-hydroxybenzyl)piperidine (Compound No. **2141**) (17.6 mg, quant.): The purity was determined by RPLC/MS (85%); ESI/MS m/e 448.3 (M^++H, $C_{22}H_{27}F_2N_5O_3$).

Examples 1828-1831.

The compounds of this invention were synthesized pursuant to methods of Examples 1826 and 1827 using the corresponding reactants respectively.

Preparative TLC (SiO_2), if needed, afforded the desired material. The ESI/MS data and yields of last step are summarized in Table 41.

Table 41

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 1828	2140	C23 H27 F2 N5 O4	476.3	6.7	28.4
Example 1829	2144	C24 H30 F3 N5 O3	494.2	18.7	82.0
Example 1830	2145	C23 H28 F3 N5 O3	480.3	19.8	63.7
Example 1831	2146	C24 H28 F3 N5 O4	508.3	13.5	81.7

Example 1832: Preparation of 1-(3-Amino-4-chlorobenzyl)-4-[{*N*-(2-(*tert* butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl}aminomethyl]piperidine.

To a mixture of 4-[{*N*-(2-(*tert*-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl}aminomethyl]piperidine (0.14 mmol), 4-chloro-3-nitrobenzaldehyde (0.50 mmol), methanol (1.5 mL), and acetic acid (0.070 mL) was added $NaBH_3CN$ (0.63 mmol) in methanol (1.3 mL). The reaction mixture was stirred at 50 °C overnight. The mixture was cooled to room temperature, loaded onto Varian™ SCX column, and washed with CH_3OH. Product was eluted off using 2 N NH_3 in CH_3OH and concentrated. The resulting material was dissolved into ethyl acetate/methanol = 5/1, loaded onto Varian™ Si column, eluted off using ethyl acetate/methanol = 5/1 (6 mL), and concentrated to give 4-[{*N*-(2-(*tert*-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl}aminomethyl]-1-(4-chloro-3-nitrobenzyl)piperidine (44 mg, 53%): ESI/MS m/e 596.3 (M^++H).

A mixture of 4-[{*N*-(2-(*tert*-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl}aminomethyl]-1-(4-chloro-3-nitrobenzyl)piperidine (121 mg, 0.20 mmol), 10% palladium-activated carbon (85 mg), ethyl acetate (10 mL), and methanol (1 mL) was stirred under a hydrogen atmosphere at room temperature for 19 h. The Pd catalyst was filtered off and the filtrate was concentrated to afford 1-(3-amino-4-chlorobenzyl)-4-[{*N*-(2-(*tert*-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl}aminomethyl]piperidine (78 mg, 68%).

Example 1833: Preparation of 1-(3-Amino-4-chlorobenzyl)-4-[{*N*-(2-amino-4,5-difluorobenzoyl)glycyl}aminomethyl]piperidine (Compound No. 2142).

The titled compound, 1-(3-amino-4-chlorobenzyl)-4-[{*N*-(2-amino-4,5-difluorobenzoyl)glycyl}aminomethyl]piperidine (Compound No. **2142**) was synthesized pursuant to method of Example 1832 using the corresponding reactant:

13.7 mg, 98%); The purity was determined by RPLC/MS (83%); ESI/MS m/e 466.2 (M^{+}+H, $C_{22}H_{26}ClF_2N_5O_2$).

Example 1834: Preparation of 1-(3-Acetylamino-4-hydroxybenzyl)-4-[{*N*-(2-amino-4,5-difluorobenzoyl)glycyl}aminomethyl]piperidine (Compound No. 2148).

To a mixture of 1-(3-amino-4-hydroxybenzyl)-4-[{*N*-(2-(*tert*-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl}aminomethyl]piperidine (27 mg, 0.049 mmol), (piperidinomethyl)polystyrene (2.7 mmol/g, 60 mg, 0.15 mmol) and dichloromethane (2 mL) was added acetic anhydride (0.12 mmol) in dichloromethane (0.12 mL). The reaction mixture was stirred at room temperature for 3 h. The mixture was loaded onto Varian™ SCX column, and washed with CH_3OH. Product was eluted off using 2 N NH_3 in CH_3OH and concentrated to give 1-(3-acetylamino-4-hydroxybenzyl)-4-[{*N*-(2-(*tert*-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl}aminomethyl]piperidine (30 mg, quant.): ESI/MS m/e 590.4 (M^{+}+H, $C_{29}H_{37}F_2N_5O_6$).

To a solution of 1-(3-acetylamino-4-hydroxybenzyl)-4-[{*N*-(2-(*tert*-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl}aminomethyl]piperidine obtained above in methanol (1 mL) was added 4 N HCl in dioxane (0.50 mL) and the solution was stirred at room temperature overnight. After the solution was concentrated, the residue was dissolved in methanol, loaded onto Varian™ SCX column, washed with CH_3OH (5 mL x 2), and eluted off using 2 N NH_3 in CH_3OH (5 mL). Concentration and preparative TLC (SiO_2, AcOEt/MeOH = 3:2) afforded 1-(3-acetylamino-4-hydroxybenzyl)-4-[{*N*-(2-amino-4,5-difluorobenzoyl)glycyl}aminomethyl]piperidine (Compound No. **2148**) (2.3 mg, 9.2%): The purity was determined by RPLC/MS (98%); ESI/MS m/e 490.3 (M^{+}+H, $C_{24}H_{29}F_2N_5O_4$).

Examples 1835-1839.

The compounds of this invention were synthesized pursuant to methods of Examples 1826 and 1834 using the corresponding reactants respectively. The ESI/MS data and yields are summarized in Table 42.

Table 42

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 1835	2143	C25 H29 F2 N5 O5	518.3	4.8	45
Example 1836	2147	C25 H31 F2 N5 O4	504.3	3.0	23
Example 1837	2154	C26 H32 F3 N5 O4	536.4	4.1	66
Example 1838	2155	C25 H30 F3 N5 O4	522.3	5.5	71
Example 1839	2156	C26 H30 F3 N5 O5	550.3	7.0	78

Example 1840: Preparation of 4-[{*N*-(2-Amino-4,5-difluorobenzoyl)glycyl}aminomethyl]-1-(3-methylamino-4-hydroxybenzyl)piperidine (Compound No. 2160).

To a mixture of 4-[{*N*-(2-(*tert*-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl}aminomethyl]-1-(3-amino-4-hydroxybenzyl)piperidine (20.4 mg, 0.037 mmol), 37% HCHO solution (3.0 mg, 0.037 mmol), acetic acid (0.10 mL) and methanol (1.3 mL) was added $NaBH_3CN$ (7.0 mg) in methanol (0.2 mL). The reaction mixture was stirred at 60 °C overnight. The mixture was cooled to room temperature, loaded onto Varian™ SCX column, and washed with CH_3OH (5 mL x 2). Product was eluted off using 2 N NH_3 in CH_3OH (8 mL) and concentrated to give 4-[{*N*-(2-(*tert*-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl}aminomethyl]-1-(3-methylamino-4-hydroxybenzyl)piperidine.

To a solution of 4-[{*N*-(2-(*tert*-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl}aminomethyl]-1-(3-methylamino-4-hydroxybenzyl)piperidine obtained above in methanol (1.0 mL) was added 4 N HCl in dioxane (1.0 mL) and the solution was stirred at room temperature for 3 h. After the solution was concentrated, the residue was dissolved in methanol (1 mL), loaded onto Varian™ SCX column, washed with CH_3OH (5 mL x 2), and eluted off using 2 N NH_3 in CH_3OH (8 mL). Concentration and preparative TLC (SiO_2) afforded 4-[{*N*-(2-amino-4,5-difluorobenzoyl)glycyl}aminomethyl]-1-(3-methylamino-4-hydroxybenzyl)piperidine (Compound No. **2160**) (3.4 mg, 20%): The purity was determined by RPLC/MS (96%); ESI/MS m/e 462.4 (M^++H, $C_{23}H_{29}F_2N_5O_3$).

Examples 1841-1844.

The compounds of this invention were synthesized pursuant to methods of Examples 1826 and 1840 using the corresponding reactants respectively. The ESI/MS data and yields are summarized in Table 43.

Table 43

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 1841	2159	C24 H31 F2 N5 O3	476.3	7.6	48
Example 1842	2161	C23 H28 Cl F2 N5 O2	480.3	7.3	45
Example 1843	2162	C25 H32 F3 N5 O3	508.4	6.0	24
Example 1844	2163	C24 H30 F3 N5 O3	494.3	4.3	15

Example 1845: Preparation of 4-[{*N*-(2-Amino-4,5-difluorobenzoyl)glycyl}aminomethyl]-1-(benzo[c]furazan-5-yl)piperidine (Compound No. 2130).

A mixture of 4-[{*N*-(2-(*tert*-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl}aminomethyl]piperidine (0.050 mmol), 5-(bromomethyl)benzo[c]furazan (0.75 mmol), (piperidinomethyl)polystyrene (2.6-2.8 mmol/g, 60 mg, 0.15 mmol), methanol (0.2 mL), acetonitrile (1.0 mL), and chloroform (0.50 mL) was stirred at 50 °C overnight. The mixture was cooled to room temperature, loaded onto Varian™ SCX column, and washed with CH_3OH (5 mL x 2). Product was eluted off using 2 N NH_3 in CH_3OH (5 mL) and concentrated. To the resulting material were added chloroform (1.5 mL) and phenyl isocyanate (0.075 mL) and the solution was stirred at room temperature for 1 h, loaded onto Varian™ SCX column, and washed with CH_3OH (5 mL x 2). Product was eluted off using 2 N NH_3 in CH_3OH (5 mL) and concentrated. The residue was dissolved in methanol (1 mL) and 4 N HCl in dioxane (0.50 mL) was added. The solution was stirred at room temperature overnight and concentrated. The residue was dissolved in methanol, loaded onto Varian™ SCX column, washed with CH_3OH (5 mL x 2), and eluted off using 2 N NH_3 in CH_3OH (5 mL). Concentration and preparative TLC (SiO_2, ethyl acetate/MeOH = 5/1) afforded 4-[{*N*-(2-amino-4,5-difluorobenzoyl)glycyl}aminomethyl]-1-(benzo[c]furazan-5-yl)piperidine (Compound No. **2130**) (3.6 mg, 16%): The purity was determined by RPLC/MS (87%); ESI/MS m/e 459.3 (M^++H, $C_{22}H_{24}F_2N_6O_3$).

Example 1846: Preparation of 4-[{*N*-(2-Amino-4,5-difluorobenzoyl)glycyl}aminomethyl]-1-(3,5-dimethylisoxazol-4-yl)piperidine (Compound No. 2131).

The titled compound, 4-[{*N*-(2-amino-4,5-difluorobenzoyl)glycyl}aminomethyl]-1-(3,5-dimethylisoxazol-4-yl)piperidine (Compound No. **2131**), was synthesized pursuant to methods of Example 1845 using the corresponding reactant: 3.8 mg, 18% yield; ESI/MS m/e 436.2 (M^++H, $C_{21}H_{27}F_2N_5O_3$).

Example 1847: Preparation of 4-[{*N*-(2-Amino-5-chlorobenzoyl)glycyl}aminomethyl]-1-{4-(trifluoromethylthio)benzyl}piperidine (Compound No. 1616).

A mixture of 4-[{*N*-(2-amino-5-chlorobenzoyl)glycyl}aminomethyl]piperidine (16.2 mg, 0.050 mmol), 4-(trifluoromethylthio)benzyl bromide (20.3 mg, 0.075 mmol), piperidinomethyl-polystyrene (60 mg), acetonitrile (1.0 mL) and chloroform (0.50 mL) was stirred at 60 °C for 15 h. The reaction mixture was cooled, loaded onto Varian™ SCX column and washed with CH_3OH (15 mL). Product was eluted using 2 N NH_3 in CH_3OH (5 mL) and concentrated to afford 4-[{*N*-(2-amino-5-chlorobenzoyl)glycyl}aminomethyl]-1-{4-(trifluoromethylthio)benzyl}piperidine (Compound No. **1616**) (21.9 mg, 85%): The purity was determined by RPLC/MS (96%); ESI/MS m/e 545.2 (M^++H, $C_{23}H_{26}ClF_3N_4O_2S$).

Example 1848-1868.

The compound of this invention was synthesized pursuant to methods of Example 1847 using the corresponding reactant. Preparative TLC, if needed, afforded the desired material. The ESI/MS data and yields are summarized in Table 44.

Table 44

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 1848	1617	C23 H26 Br F3 N4 O2 S	559.0	21.0	75
Example 1849	1777	C23 H25 Cl2 F3 N4 O2	517.0	16.3	63.0
Example 1850	1778	C24 H29 F3 N4 O2	463.2	9.5	41.1
Example 1851	1779	C24 H27 F3 N4 O4	493.2	12.7	51.6
Example 1852	1780	C23 H26 Br F3 N4 O2	527.0	16.4	62.2
Example 1853	1781	C23 H27 F3 N4 O3	465.2	10.0	28.7
Example 1854	1782	C25 H29 F3 N4 O2	475.2	12.2	34.3
Example 1855	1783	C24 H26 F3 N5 O2	474.2	17.2	48.4
Example 1856	1784	C23 H27 F3 N4 O2	449.2	11.3	33.6
Example 1857	1788	C25 H31 F3 N4 O2	477.2	10.0	42.0
Example 1858	1789	C24 H29 F3 N4 O3	479.2	10.0	27.9
Example 1859	1792	C24 H30 F2 N4 O2	445.2	5.9	26.5
Example 1860	1793	C22 H24 Cl2 F2 N4 O2	485.2	9.2	37.9
Example 1861	1794	C23 H28 F2 N4 O2	431.2	5.7	26.5
Example 1862	1795	C23 H26 F2 N4 O4	461.2	6.0	26.1

Example 1863	1796	C22 H25 Br F2 N4 O2	497.0	10.5	42.4
Example 1864	1797	C22 H26 F2 N4 O3	433.2	3.5	16.2
Example 1865	1798	C23 H28 F2 N4 O3	447.2	5.6	25.1
Example 1866	1799	C24 H28 F2 N4 O2	443.2	5.5	24.9
Example 1867	1800	C23 H25 F2 N5 O2	442.2	9.4	42.6
Example 1868	1801	C22 H26 F2 N4 O2	417.2	6.5	31.2

Example 1869: Preparation of 4-[{*N*-(2-Amino-5-trifluoromethoxybenzoyl)glycyl}aminomethyl]-1-(4-bromobenzyl)piperidine (Compound No. 1910).

A mixture of 4-[{*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethoxybenzoyl)glycyl}aminomethyl]piperidine (0.050 mmol), 4-bromobenzyl bromide (0.060 mmol), piperidinomethylpolystyrene (60 mg), acetonitrile (0.8 mL) and chloroform (0.5 mL) was stirred at 60 °C for 12 h. The reaction mixture was cooled, loaded onto Varian™ SCX column and washed with 50% $CHCl_3/CH_3OH$ (10 mL) and CH_3OH (10 mL). Product was eluted using 2 N NH_3 in CH_3OH (5 mL) and concentrated. To the resulting material was added 4 N HCl in 1,4-dioxane (2 mL), and the solution was stirred overnight at room temperature. Concentration and preparative TLC afforded 4-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}aminomethyl]-1-(4-bromobenzyl)piperidine (Compound No. **1910**) (6.5 mg, 24%): The purity was determined by RPLC/MS (96%); ESI/MS m/e 545 (M^{+}+H, $C_{23}H_{26}BrF_3N_4O_3$).

Examples 1870-1873.

The compounds of this invention were synthesized pursuant to methods of Example 1869 using the corresponding reactant respectively. The ESI/MS data and yields are summarized in Table 45.

Table 45

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 1870	1911	C23 H25 Cl2 F3 N4 O3	533	10.6	39.7
Example 1871	1912	C23 H27 F3 N4 O4	481	12.5	52.0
Example 1872	1913	C25 H31 F3 N4 O3	493	7.5	30.5
Example 1873	1914	C24 H29 F3 N4 O3	479	11.0	46.0

Example 1874: Preparation of 4-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}aminomethyl]-1-(benz[d]imidazol-5-

yl)piperidine (Compound No. 2186).

A mixture of 4-[{*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}aminomethyl]piperidine (0.060 mmol), 1-(*tert*-butoxycarbonyl)-6-(bromomethyl)benz[d]imidazole (15.6 mg, 0.050 mmol), (piperidinomethyl)polystyrene (86 mg), and acetonitrile (2 mL) was stirred at 50 °C for 3 h. After cooling to room temperature, phenyl isocyanate (30 mg) was added and the mixture was stirred at room temperature for 1 h, loaded onto Varian™ SCX column and washed with CH_3OH (5 mL) and $CHCl_3$ (5 mL). Product was eluted using 2 N NH_3 in CH_3OH (3 mL) and concentrated.

The resulting material was dissolved into methanol (1 mL), and 4 N HCl in dioxane (1 mL) was added. The solution was stirred at room temperature overnight, loaded onto Varian™ SCX column and washed with CH_3OH and dichloromethane. Product was eluted using 2 N NH_3 in CH_3OH and concentrated. Preparative TLC (SiO_2, AcOEt/MeOH = 3:1) afforded 4-[{*N*-(2-amino-5-trifluorobenzoyl)glycyl}aminomethyl]-1-(benz[d]imidazol-5-yl)piperidine (Compound No. **2186**) (1.9 mg, 7.8%): The purity was determined by RPLC/MS (100%); ESI/MS m/e 489.4 (M^{+}+H, $C_{24}H_{27}F_3N_6O_2$).

Example 1875: Preparation of 4-[{*N*-(2-Amino-4,5-difluorobenzoyl)glycyl}aminomethyl]-1-(benzo[c]thiadiazol-5-yl)piperidine (Compound No. 2184).

To a mixture of 5-(hydroxymethyl)benzo[c]thiadiazole (8.3 mg, 0.050 mmol), (piperidinomethyl)polystyrene (86 mg), and chloroform (1 mL) was added methanesulfonyl chloride (0.0042 mL) and the mixture was stirred at room temperature for 1.5 h. Acetonitrile (1 mL) and 4-[{*N*-(2-(*tert*-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl}aminomethyl]piperidine (0.060 mmol) was added and the reaction mixture was stirred at 50 °C for 3 h. After cooling to room temperature, phenyl isocyanate (30 mg) was added, and the mixture was stirred at room temperature for 1 h, loaded onto Varian™ SCX column and washed with CH_3OH (5 mL) and $CHCl_3$ (5 mL). Product was eluted using 2 N NH_3 in CH_3OH (3 mL) and concentrated.

The resulting material was dissolved into dichloromethane (1 mL), and 1 M chlorotrimethylsilane and 1 M phenol in dichloromethane (1 mL) was added. The solution was stirred at room temperature for 5 h, loaded onto Varian™ SCX column and washed with CH_3OH and dichloromethane. Product was eluted using 2 N NH_3 in CH_3OH and concentrated. Preparative TLC (SiO_2, AcOEt/MeOH = 3:1) afforded 4-[{*N*-(2-amino-4,5-difluorobenzoyl)glycyl}aminomethyl]-1-(benzo[c]thiadiazol-5-yl)piperidine (Compound No. **2184**) (1.3 mg, 5.5%): The

purity was determined by RPLC/MS (100%); ESI/MS m/e 475.2 (M^++H, $C_{22}H_{24}F_2N_6O_2S$).

Example 1876: Preparation of 4-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}aminomethyl]-1-(benzo[c]thiadiazol-5-yl)piperidine (Compound No. 2185).

The titled compound, 4-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}aminomethyl]-1-(benzo[c]thiadiazol-5-yl)piperidine (Compound No. **2185**) was synthesized pursuant to methods of Example 1875 using the corresponding reactant: 7.2 mg, 28% yield; ESI/MS m/e 507.4 (M^++H, $C_{23}H_{25}F_3N_6O_2S$).

Example 1877: Preparation of 4-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}aminomethyl]-1-(2-amino-4-chlorobenzyl)piperidine (Compound No. 1919).

A mixture of 4-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}aminomethyl]piperidine (0.050 mmol), 4-chloro-2-nitrobenzyl chloride (0.050 mmol), piperidinomethylpolystyrene (60 mg), acetonitrile (1.0 mL) and chloroform (0.7 mL) was stirred overnight at 50 °C. The reaction mixture was cooled, loaded onto Varian™ SCX column and washed with 50% $CHCl_3/CH_3OH$ (10 mL) and CH_3OH (10 mL). Product was eluted using 2 N NH_3 in CH_3OH (5 mL) and concentrated. To the resulting material was added ethanol (3 mL) and 10% Pd-C (15 mg), and the mixture was stirred under H_2 at room temperature for 1.5 h. Filtration, concentration, and preparative TLC afforded 4-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}aminomethyl]-1-(2-amino-4-chlorobenzyl)piperidine (Compound No. **1919**) (5.1 mg, 14%): The purity was determined by RPLC/MS (90%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09-1.32 (m, 4 H), 1.41-1.59 (m, 1 H), 1.66 (d, J = 12.5 Hz, 2 H), 1.88 (t, J = 11.5 Hz, 2 H), 2.82 (d, J = 11.5 Hz, 2 H), 3.17 (t, J = 6.5 Hz, 2 H), 3.42 (s, 2 H), 4.05 (d, J = 5.5 Hz, 2 H), 4.85 (br s, 1 H), 5.92 (br s, 2 H), 6.25-6.36 (m, 1 H), 6.55-6.66 (m, 1 H), 6.70 (d, J = 8.5 Hz, 1 H), 6.85 (d, J = 8.5 Hz, 1 H), 7.26 (s, 1 H), 7.42 (d, J = 8.5 Hz, 1 H), 7.68 (s, 1 H) ;ESI/MS m/e 498.2 (M^++H, $C_{23}H_{27}ClF_3N_5O_2$).

Examples 1878 and 1879.

The compounds of this invention were synthesized pursuant to methods of Example 1877 using the corresponding reactant respectively. The ESI/MS data and yields are summarized in Table 46.

Table 46

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 1878	1920	C22 H26 Cl F2 N5 O2	466.2	3.5	10.0
Example 1879	1922	C23 H27 Cl F3 N5 O3	514.2	1.2	3.1

Example 1880: Preparation of 4-[{*N*-(2-Amino-5-trifluoromethylbenzoyl)glycyl}aminomethyl]-1-(benz[d]oxazol-5-yl)piperidine (Compound No. 2188).

A solution of 1-(3-amino-4-hydroxybenzyl)-4-[{*N*-(2-(*tert*-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl}aminomethyl]piperidine (34.8 mg, 0.060 mmol), prepared pursuant to methods of Example 1826, in THF (2 mL) was treated with triethyl orthoformate (0.033 mL, 3.3 eq) and pyridinium *p*-toluenesulphonate (2 mg, 0.4 eq). The reaction mixture was stirred overnight under reflux. After cooling to room temperature, the mixture was concentrated. The residue was dissolved in AcOEt, loaded onto BondElut™ Si column, eluted off using ethyl acetate/methanol = 4/1, and concentrated.

The resulting material was dissolved into AcOEt (1.5 mL), and 4 N HCl in dioxane (0.5 mL) was added. The solution was stirred at room temperature overnight, adjusted to pH 10 with 5 M NaOH aqueous solution, and extracted with AcOEt. The extract was concentrated and purified by PTLC (SiO_2, AcOEt/MeOH = 4:1) to afford 4-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}aminomethyl]-1-(benz[d]oxazol-5-yl)piperidine (Compound No. **2188**) (1.6 mg, 5%): The purity was determined by RPLC/MS (94%); ESI/MS m/e 490.3 (M^++H, $C_{24}H_{26}F_3N_5O_3$).

Example 1881: Preparation of 4-[{*N*-(2-Amino-4,5-difluorobenzoyl)glycyl}aminomethyl]-1-(2-oxo-2,3-dihydro-1,3-benzoxazol-5-yl)piperidine (Compound No. 2190).

To a mixture of 1-(3-amino-4-hydroxy)-4-[{*N*-(2-(*tert*-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl}aminomethyl]piperidine (22 mg, 0.040 mmol), $NaHCO_3$ (0.040 mmol), water (0.7 mL), and methanol (1.5 mL) was added phenyl chloroformate (0.046 mmol) and the mixture was stirred at room temperature for 3 h. A 1 N NaOH solution (0.040 mL) was added, and the reaction mixture was stirred for additional 1.5 h. The mixture was extracted with ethyl acetate and evaporated. The residue was dissolved in methanol, loaded onto Varian™ SCX column and washed with CH_3OH (5 mL x 2). Product was eluted using 2 N NH_3 in CH_3OH (5 mL) and concentrated.

To the resulting material was added 1 M chlorotrimethylsilane and 1 M

phenol in dichloromethane (2 mL). The solution was stirred at room temperature for 2 h and evaporated. The residue was dissolved in methanol, loaded onto Varian™ SCX column and washed with CH_3OH (5 mL x 2). Product was eluted using 2 N NH_3 in CH_3OH (5 mL) and concentrated. Preparative TLC (SiO_2, AcOEt/MeOH = 5:2) afforded 4-[{*N*-(2-amino-4,5-difluorobenzoyl)glycyl}aminomethyl]-1-(2-oxo-2,3-dihydro-1,3-benzoxazol-5-yl)piperidine (Compound No. **2190**) (4.1 mg, 22%): The purity was determined by RPLC/MS (100%); ESI/MS m/e 474.2 (M^++H, $C_{23}H_{25}F_2N_5O_4$).

Examples 1882-1884.

The compounds of this invention were synthesized pursuant to methods of Example 1881 using the corresponding reactant respectively (phenyl chlorothionoformate was used instead of phenyl chloroformate for preparation of Compounds **2192** and **2193**). The ESI/MS data and yields are summarized in Table 47.

Table 47

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 1882	2191	C24 H26 F3 N5 O4	506.3	3.1	10
Example 1883	2192	C23 H25 F2 N5 O3 S	490.2	6.9	35
Example 1884	2193	C24 H26 F3 N5 O3 S	522.2	3.6	11

Reference Example 36: Preparation of 4-[{*N*-(1-(9-Fuluorenylmethoxycarbonyl)piperidine-4-ylmethyl)carbamoylmethyl}aminomethyl]-3-methoxyphenyloxymethyl-polystyrene.

To a solution of 1-(9-fuluorenylmethoxycarbonyl)-4-(glycylaminomethyl)piperidine hydrochloride (10 mmol) in DMF (65 mL) were added acetic acid (0.3 mL), sodium triacetoxyborohydride (1.92 g), and 4-formyl-3-(methoxyphenyloxymethyl)-polystyrene (1 mmol/g, 200 g). The mixture was shaken for 2 h and filtered. The resin was washed with MeOH, DMF, CH_2Cl_2, and methanol, and dried to afford the desired material.

Examples 1885-2000: General Procedure for Solid-Phase Synthesis of 4-Aminomethylpiperidines.

To a mixture of the corresponding acid (1.6 mmol), HBTU (1.6 mmol), and DMF (6 mL) was added diisopropylethylamine (3.6 mmol), and the mixture was shaken

for 2 min. 4-[{*N*-(1-(9-fuluorenylmethoxycarbonyl)piperidine-4-ylmethyl)carbamoylmethyl}aminomethyl]-3-methoxyphenyloxymethyl-polystyrene (0.4 mmol) was added and the mixture was shaken for 1 h and filtered. The resin was rinsed with DMF and CH_2Cl_2, and dried.

A mixture of the resulting resin, piperidine (3.2 mL), and DMF (12.8 mL) was shaken for 10 min and filtered. The resin was washed with DMF and CH_2Cl_2, and dried.

To the dry resin (0.05 mmol) was added a mixture of $NaBH(OAc)_3$ (0.25 mmol), AcOH (0.025 mL) and DMF (1 mL). The corresponding aldehyde (2.5 mmol) was added, and the mixture was shaken for 2 h, then filtered and washed with CH_3OH, 10% diisopropylethylamine in DMF, DMF, CH_2Cl_2, and CH_3OH. A mixture of the resin, water (0.050 mL), and trifluoroacetic acid (0.95 mL) was shaken for 1 h and filtered. The resin was washed with CH_2Cl_2 and CH_3OH. The filtrate and washings were combined and concentrated. The crude material was loaded onto Varian™ SCX column and washed with CH_3OH (15 mL). Product was eluted using 2 N NH_3 in CH_3OH (5 mL) and concentrated. Preparative TLC or HPLC, if needed, afforded the desired material. The ESI/MS data and yields are summarized in Table 48.

Table 48

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 1885	1923	C23 H25 Br F3 N3 O2 S	544	15.7	87
Example 1886	1924	C24 H28 F3 N3 O3 S	496	14.6	89
Example 1887	1925	C23 H25 F4 N3 O2 S	484	11.7	73
Example 1888	1926	C23 H24 F5 N3 O2 S	502	13.9	84
Example 1889	1927	C23 H26 F3 N3 O3 S	482	10.7	67
Example 1890	1928	C24 H26 F3 N3 O4 S	510	14.3	85
Example 1891	1929	C26 H30 F3 N3 O2 S	506	14.7	88
Example 1892	1930	C24 H28 F3 N3 O2 S2	512	14.4	85
Example 1893	1931	C25 H30 F3 N3 O2 S	494	14.3	88
Example 1894	1932	C25 H28 F3 N3 O3 S	509	7.1*	35
Example 1895	1933	C25 H30 F3 N3 O2 S	494	14.3	88
Example 1896	1934	C26 H32 F3 N3 O2 S	509	14.4	86
Example 1897	1935	C23 H25 F3 N4 O4 S	511	14.9	88
Example 1898	1936	C24 H28 F3 N3 O2 S	480	13.3	84
Example 1899	1937	C26 H32 F3 N3 O2 S	509	11.1	66
Example 1900	1938	C23 H27 Br2 N3 O2	538	5.3*	25
Example 1901	1939	C24 H30 Br N3 O3	488	5.0*	25

Example 1902	1940	C23 H27 Br F N3 O2	476	4.9*	25
Example 1903	1941	C23 H26 Br F2 N3 O2	494	6.1*	30
Example 1904	1942	C23 H28 Br N3 O3	474	1.7*	9
Example 1905	1943	C24 H28 Br N3 O4	502	6.6*	32
Example 1906	1944	C26 H32 Br N3 O2	498	7.0*	35
Example 1907	1945	C24 H30 Br N3 O2 S	504	11.1	67
Example 1908	1946	C25 H32 Br N3 O2	488	3.2*	16
Example 1909	1947	C25 H30 Br N3 O3	500	5.7	35
Example 1910	1948	C25 H32 Br N3 O2	486	4.9*	25
Example 1911	1949	C26 H34 Br N3 O2	500	6.7*	33
Example 1912	1950	C23 H27 Br N4 O4	503	5.0*	25
Example 1913	1951	C24 H30 Br N3 O2	472	5.1*	26
Example 1914	1952	C22 H24 Br2 F N3 O2	542	14.9	83
Example 1915	1953	C23 H27 Br F N3 O3	492	13.9	86
Example 1916	1954	C22 H24 Br F2 N3 O2	480	12.5	79
Example 1917	1955	C22 H23 Br F3 N3 O2	498	13.2	80
Example 1918	1956	C22 H25 Br F N3 O3	478	7.0	44
Example 1919	1957	C23 H25 Br F N3 O4	506	4.0*	20
Example 1920	1958	C25 H29 Br F N3 O2	502	14.6	88
Example 1921	1959	C23 H27 Br F N3 O2 S	508	13.1	78
Example 1922	1960	C24 H29 Br F N3 O2	490	13.8	85
Example 1923	1961	C24 H27 Br F N3 O3	504	2.7*	13
Example 1924	1962	C24 H29 Br F N3 O2	490	12.7	78
Example 1925	1963	C25 H31 Br F N3 O2	504	13.5	81
Example 1926	1964	C22 H24 Br F N4 O4	507	14.8	88
Example 1927	1965	C23 H27 Br F N3 O2	476	12.1	77
Example 1928	1966	C25 H31 Br F N3 O2	504	13.4	80
Example 1929	1967	C22 H26 Br F N4 O2	477	4.7*	20
Example 1930	1968	C23 H29 F N4 O3	429	6.9*	32
Example 1931	1969	C22 H27 F N4 O3	415	3.7*	17
Example 1932	1970	C23 H27 F N4 O4	443	5.4*	24
Example 1933	1971	C25 H31 F N4 O2	439	4.3*	20
Example 1934	1972	C23 H29 F N4 O2 S	445	6.2*	28
Example 1935	1973	C24 H31 F N4 O2	427	6.3*	29
Example 1936	1974	C24 H31 F N4 O2	427	4.9*	23
Example 1937	1975	C22 H26 F N5 O4	444	5.9*	27
Example 1938	1976	C23 H29 F N4 O2	413	6.7*	32
Example 1939	1977	C23 H26 F N5 O2	424	5.1*	24
Example 1940	1978	C25 H33 F N4 O2	441	6.3*	29
Example 1941	1979	C25 H30 F2 N4 O2	457	8.0*	35

Example 1942	1980	C24 H28 F2 N4 O3	459	6.0*	26
Example 1943	1981	C22 H25 F2 N5 O4	462	9.3*	41
Example 1944	1982	C23 H25 F2 N5 O2	442	6.0*	27
Example 1945	1983	C25 H32 F2 N4 O2	459	8.3*	37
Example 1946	1984	C22 H26 Br I N4 O2	585	9.7*	36
Example 1947	1985	C23 H29 I N4 O3	537	9.2*	36
Example 1948	1986	C22 H27 I N4 O3	523	5.8*	23
Example 1949	1987	C23 H27 I N4 O4	551	8.2*	32
Example 1950	1988	C25 H31 I N4 O2	547	6.7*	26
Example 1951	1989	C23 H29 I N4 O2 S	553	6.4*	25
Example 1952	1990	C24 H31 I N4 O2	535	7.2*	29
Example 1953	1991	C24 H29 I N4 O3	549	5.6*	22
Example 1954	1992	C24 H31 I N4 O2	535	6.2*	25
Example 1955	1993	C22 H26 I N5 O4	552	10.2*	40
Example 1956	1994	C23 H29 I N4 O2	521	7.5*	30
Example 1957	1995	C23 H26 I N5 O2	532	6.8*	27
Example 1958	1996	C25 H33 I N4 O2	549	7.1*	28
Example 1959	1997	C25 H33 I N4 O2	549	3.0*	12
Example 1960	1998	C22 H25 Br Cl N3 O2	478	7.6*	39
Example 1961	1999	C23 H28 Cl N3 O3	430	7.0*	39
Example 1962	2000	C22 H25 Cl F N3 O2	418	14.1	102
Example 1963	2001	C22 H26 Cl N3 O3	416	6.3*	36
Example 1964	2002	C23 H26 Cl N3 O4	444	7.1*	39
Example 1965	2003	C25 H30 Cl N3 O2	440	15.3	105
Example 1966	2004	C23 H28 Cl N3 O2 S	446	8.4*	45
Example 1967	2005	C24 H30 Cl N3 O2	428	7.4*	41
Example 1968	2006	C24 H30 Cl N3 O2	428	13.8	98
Example 1969	2007	C22 H25 Cl N4 O4	445	16.0	109
Example 1970	2008	C23 H28 Cl N3 O2	414	14.1	103
Example 1971	2009	C23 H25 Cl N4 O2	425	14.8	106
Example 1972	2010	C25 H32 Cl N3 O2	442	14.5	99
Example 1973	2011	C25 H32 Cl N3 O2	442	14.5	99
Example 1974	2012	C22 H24 Br2 Cl N3 O2	558	12.8*	58
Example 1975	2013	C23 H27 Br Cl N3 O3	508	8.6*	42
Example 1976	2014	C22 H25 Br Cl N3 O3	494	6.0*	30
Example 1977	2015	C23 H25 Br Cl N3 O4	522	8.4*	40
Example 1978	2016	C25 H29 Br Cl N3 O2	518	17.6	103
Example 1979	2017	C23 H27 Br Cl N3 O2 S	524	17.1	99
Example 1980	2018	C24 H29 Br Cl N3 O2	506	14.7	88
Example 1981	2019	C24 H27 Br Cl N3 O3	520	8.0*	38

Example 1982	2020	C24 H29 Br Cl N3 O2	506	14.7	88
Example 1983	2021	C22 H24 Br Cl N4 O4	523	12.0*	57
Example 1984	2022	C23 H27 Br Cl N3 O2	492	8.5*	42
Example 1985	2023	C23 H24 Br Cl N4 O2	503	6.3*	31
Example 1986	2024	C25 H31 Br Cl N3 O2	520	9.6*	46
Example 1987	2025	C25 H31 Br Cl N3 O2	520	15.0	87
Example 1988	2026	C22 H23 Br Cl F2 N3 O2	514	15.8	93
Example 1989	2027	C22 H26 Br2 N4 O2	537	10.7*	42
Example 1990	2028	C23 H29 Br N4 O3	489	8.5*	36
Example 1991	2029	C22 H27 Br N4 O3	475	7.5*	32
Example 1992	2030	C23 H27 Br N4 O4	503	6.8*	28
Example 1993	2031	C25 H31 Br N4 O2	499	6.2*	26
Example 1994	2032	C24 H29 Br N4 O3	501	8.9*	37
Example 1995	2033	C24 H31 Br N4 O2	487	9.1*	39
Example 1996	2034	C22 H26 Br N5 O4	504	6.4*	26
Example 1997	2035	C23 H29 Br N4 O2	473	6.5*	28
Example 1998	2036	C23 H26 Br N5 O2	484	6.3*	27
Example 1999	2037	C25 H33 Br N4 O2	501	5.4*	22
Example 2000	2038	C22 H25 Br F2 N4 O2	495	5.4*	23

*Yield of TFA salt.

Example 2001: Preparation of 1-(3-Carbamoylbenzyl)-4-[{*N*-(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine (Compound No. 924).

EDCI (10.7 mg), 1-hydroxybenzotriazole hydrate (7.5 mg), Et_3N (15.4 mg), 0.5 M NH_3 in dioxane (0.1 mL, 0.05 mmol) and DMF (0.5 mL) were added to a solution of 1-(3-carboxybenzyl)-4-[{*N*-(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine (19.4 mg, 0.041 mmol) in $CHCl_3$ (2.5 mL). The reaction mixture was stirred at 25 °C for 20 h, washed with 2 N aqueous NaOH (2 x 2 mL) and brine (1 mL). After filtration through PTFE membrane filter, the solvent was removed under reduced pressure to afford 1-(3-carbamoylbenzyl)-4-[{*N*-(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine (compound No. **924**) as a pale yellow solid (17.9 mg, 92%): The purity was determined by RPLC/MS (89%); ESI/MS m/e 447.3 (M^++H, $C_{24}H_{27}F_3N_4O_3$).

Example 2002: Preparation of 1-(4-Carbamoylbenzyl)-4-[{*N*-(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine (Compound No. 925).

Compound No. **925** was synthesized pursuant to methods of Example 2001 using

the corresponding reactant: 14.2 mg, 72%; The purity.was determined by RPLC/MS (86%); ESI/MS m/e 447 (M^++H, $C_{24}H_{27}F_3N_4O_3$).

Example 2003: Preparation of 1-(4-Aminobenzyl)-4-[{*N*-(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine (Compound No. 516).

A solution of 1-(4-nitrobenzyl)-4-[{*N*-(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine (22.4 mg, 0.047 mmol) in EtOH (3 mL) was hydrogenated at 1 atm for 1 h in the presence of 5% palladium on charcoal (10 mg) at 25 °C. The catalyst was removed by filtration and washed with EtOH (5 mL). The combined filtrate was evaporated to afford 1-(4-aminobenzyl)-4-[{*N*-(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine (compound No. **516**) as a pale yellow solid (20.1 mg, 96%). The purity was determined by RPLC/MS (99%); ESI/MS m/e 449.1 (M^++H, $C_{23}H_{27}F_3N_4O_2$).

Examples 2004 and 2005.

Compounds No. **517** and **518** were synthesized pursuant to methods of Example 2003 using the corresponding reactant respectively. The ESI/MS data and yields are summarized in Table 49.

Table 49

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 2004	517	C23 H27 F3 N4 O2	449	26.5	78
Example 2005	518	C23 H27 F3 N4 O2	449	25.3	71

Example 2006: Preparation of 1-{4-(Benzoylamino)benzyl}-4-[{*N*-(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine (Compound No. 519).

EDCI (4.7 mg), 1-hydroxybenzotriazole hydrate (3.3 mg), Et_3N (2.5 mg) and benzoic acid (3.0 mg) were added to a solution of 1-(4-aminobenzyl)-4-[{*N*-(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine (10.1 mg, 0.023 mmol) in CH_2Cl_2 (2.5 mL). The reaction mixture was stirred at 25 °C for 16 h, washed with 2 N aqueous NaOH (2 x 2 mL) and brine (1 mL). After filtration through PTFE membrane filter, the solvent was removed under reduced pressure to afford an yellow oil which was purified by preparative TLC (SiO_2, 10% CH_3OH-CH_2Cl_2) to give 1-{4-(benzoylamino)benzyl}-4-[{*N*-(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine (compound No. **519**) as

a colorless oil (4.6 mg, 36%): The purity was determined by RPLC/MS (99%); ESI/MS m/e 553.2 (M^{+}+H, $C_{30}H_{31}F_3N_4O_3$).

Example 2007: Preparation of 1-{4-(Piperidinocarbonyl)benzyl}-4-[{*N*-(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine (Compound No. **1572**).

Piperidine (0.048 mmol), diisopropylcarbodiimide (0.45 mmol) in DMF (0.15 mL), 1-hydroxybenzotriazole hydrate (0.45 mmol) in DMF (0.15 mL) were added to a solution of 1-(4-carboxybenzyl)-4-[{*N*-(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine (0.040 mmol) in DMF (1.0 mL). The reaction mixture was stirred at room temperature for 17 h, loaded onto Varian™ SCX column, and washed with $CHCl_3/CH_3OH$ 1 : 1 (5 mL) and CH_3OH (5 mL). Product was eluted off using 2 N NH_3 in CH_3OH (5 mL) and concentrated to afford 1-{4-(piperidinocarbonyl)benzyl}-4-[{*N*-(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine (Compound No. **1572**) (14.3 mg, 66%): The purity was determined by RPLC/MS (99%); ESI/MS m/e 545 (M^{+}+H, $C_{29}H_{35}F_3N_4O_3$).

Examples 2008-2015.

The compounds of this invention were synthesized pursuant to methods of Example 2007 using the corresponding reactant respectively. The ESI/MS data and yields are summarized in Table 50.

Table 50

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 2008	1573	C31 H33 F3 N4 O4	583	17.6	76
Example 2009	1574	C31 H33 F3 N4 O3	567	18.8	83
Example 2010	1575	C30 H30 Cl F3 N4 O3	587	3.2	14
Example 2011	1576	C28 H33 F3 N4 O4	547	21.1	97
Example 2012	1577	C26 H31 F3 N4 O4	521	5.1	24
Example 2013	1578	C31 H33 F3 N4 O3	567	16.9	75
Example 2014	1579	C31 H33 F3 N4 O3	567	6.0	26
Example 2015	1580	C29 H35 F3 N4 O3	545	15.1	69

Example 2016: Preparation of 1-[4-(Chloroformyl)benzyl]-4-[{*N*-(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine.

A mixture of 1-(4-carboxybenzyl)-4-[{*N*-(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine (240 mg) and thionyl chloride (1 mL) was stirred at room temperature for 12 h and the excess thionyl chloride was removed under reduced pressure to give desired 1-[4-(chloroformyl)benzyl]-4-[{*N*-(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine. The acid chloride was used without further purification.

Example 2017: Preparation of 1-[4-{*N*-(2-Methoxyethyl)carbamoyl}benzyl]-4-[{*N*-(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine (Compound No. 1612).

A mixture of 1-[4-(chloroformyl)benzyl]-4-[{*N*-(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine (0.042 mmol), 2-methoxyethylamine (3.8 mg, 0.050 mmol), piperidinomethylpolystyrene (46 mg) and dichloromethane (1.5 mL) was stirred at room temperature for 17 h. Water (0.020 mL) was added and the mixture was stirred for 30 min. Methanol (1 mL) was added and the mixture was loaded onto Varian™ SCX column, and washed with CH_3OH (10 mL). Product was eluted off using 2 N NH_3 in CH_3OH (5 mL) and concentrated to afford 1-[4-{*N*-(2-methoxyethyl)carbamoyl}benzyl]-4-[{*N*-(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine (Compound No. **1612**) (26.7 mg, 100%): The purity was determined by RPLC/MS (92%); ESI/MS m/e 535.2 (M^++H, $C_{27}H_{33}F_3N_4O_4$).

Examples 2018-2020.

The compounds of this invention were synthesized pursuant to methods of Example 2017 using the corresponding reactant respectively. Preparative TLC, if needed, afforded the desired material. The ESI/MS data and yields are summarized in Table 51.

Table 51

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 2018	1610	C31 H30 F6 N4 O3	621.2	4.4	14
Example 2019	1611	C30 H29 Cl2 F3 N4 O3	621.2	35.7	quant
Example 2020	1613	C32 H35 F3 N4 O3	581.2	29.9	quant

Example 2021: Preparation of 4-[*N*-{5-Bromo-2-

(methylamino)benzoyl}glycyl]aminomethyl-1-(4-chlorobenzyl)piperidine (Compound No. 1427).

A solution of 4-{*N*-(2-amino-5-bromobenzoyl)glycyl}aminomethyl-1-(4-chlorobenzyl)piperidine (Compound No. **1042**) (50 mg, 0.10 mmol) in triethyl orthoformate (6.5 mL) was stirred at 150 °C for 17 h. Concentration afforded a yellow solid. To a solution of the yellow solid in ethanol (3 mL) was added sodium borohydride (7.6 mg, 0.2 mmol) and the mixture was stirred at room temperature for 14 h. A resulting white precipitate was resolved in dichloromethane and the solution was washed with 1 N aqueous NaOH (2 mL). The organic layer was separated, dried over K_2CO_3, filtered and evaporated. Column chromatography (SiO_2, 20% MeOH/$CHCl_3$) gave 4-[*N*-{5-bromo-2-(methylamino)benzoyl}glycyl]aminomethyl-1-(4-chlorobenzyl)piperidine (Compound No. **1427**) (40 mg, 80%): The purity was determined by RPLC/MS (100%); ESI/MS m/e 505 ($C_{23}H_{28}BrClF_6N_4O_2$).

Example 2022: Preparation of 4-[*N*-{5-Bromo-2-(dimethylamino)benzoyl}glycyl]aminomethyl-1-(4-chlorobenzyl)piperidine (Compound No. 1428).

Sodium cyanoborohydride (26 mg, 0.42 mmol) and acetic acid (14 μL) was added successively to a mixture of 4-{*N*-(2-amino-5-bromobenzoyl)glycyl}aminomethyl-1-(4-chlorobenzyl)piperidine (Compound No. **1042**) (67 mg, 0.14 mmol), 37% formaldehyde solution in water (0.112 mL, 1.4 mmol), acetonitrile (2 mL), and methanol (1.5 mL). After the solution was stirred at 50 °C for 30 h, 1 N aqueous NaOH and dichloromethane were added. The aqueous layer was separated and the organic layer was dried over K_2CO_3, filtered and evaporated. Column chromatography (SiO_2, 20% MeOH/AcOEt) gave 4-[*N*-{5-bromo-2-(dimethylamino)benzoyl}glycyl]aminomethyl-1-(4-chlorobenzyl)piperidine (Compound No. **1428**) (60 mg, 82%): The purity was determined by RPLC/MS (100%); ESI/MS m/e 523 ($C_{24}H_{30}BrClF_6N_4O_2$).

Example 2023: Preparation of 4-[{*N*-(5-Bromo-2-(methylsulfonylamino)benzoyl)glycyl}aminomethyl]-1-(4-chlorobenzyl)piperidine (Compound No. 1581).

A mixture of 4-[{*N*-(2-amino-5-bromobenzoyl)glycyl}aminomethyl]-1-(4-chlorobenzyl)piperidine (25 mg, 0.05 mmol), methanesulfonyl chloride (0.0045 mL), triethylamine (0.026 mL) and dichloromethane (2 mL) was stirred at room temperature for 17 h. The reaction mixture was purified with column chromatography (SiO_2), loaded onto Varian™ SAX column, and washed with CH_3OH (5

mL). Product was eluted off using 0.1 N HCl in CH_3OH (5 mL) and concentrated to afford 4-[{*N*-(5-bromo-2-(methylsulfonylamino)benzoyl)glycyl}aminomethyl]-1-(4-chlorobenzyl)-piperidine (Compound No. **1581**) (5.4 mg, 19%): ESI/MS m/e 573.0 (M^++H, $C_{23}H_{28}BrClN_4O_4S$).

Example 2024: Preparation of 4-[{*N*-(5-Bromo-2-(bis(methylsulfonyl)amino)benzoyl)glycyl}aminomethyl]-1-(4-chlorobenzyl)piperidine (Compound No. 1582).

A mixture of 1-(4-chlorobenzyl)-4-[{*N*-(2-amino-5-bromobenzoyl)glycyl}aminomethyl]piperidine (57 mg, 0.10 mmol), methanesulfonyl chloride (0.018 mL, 0.24 mmol), triethylamine (0.068 mL) and dichloromethane (2 mL) was stirred at room temperature for 8 h. Aqueous 1 N NaOH solution (1 mL) was added and the mixture was extracted with dichloromethane (2 mL x 3). The combined extracts were dried over K2CO3, filtered and evaporated. Column chromatography (SiO_2) gave 4-[{*N*-(5-bromo-2-(bis(methylsulfonyl)amino)benzoyl)glycyl}aminomethyl]-1-(4-chlorobenzyl)piperidine (Compound No. **1582**) (40 mg, 62%): ESI/MS m/e 651 (M^++H, $C_{24}H_{30}BrClN_4O_6S_2$).

Example 2025: Preparation of 1-(4-Chlorobenzyl)-1-methyl-4-[{*N*-(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidinium iodide (Methylammonium iodide of Compound No. 461).

A solution of 4-[{*N*-(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine (30 mg, 0.087 mmol) in CH_3CN (1.0 mL) and (piperidinomethyl)polystyrene (80 mg, 2.7 mmol base/g resin) were added to a solution of 4-chlorobenzyl chloride (11.7 mg, 0.073 mmol) in CH_3CN (1.0 mL). The reaction mixture was stirred at 60 °C for 2 h. Phenyl isocyanate (10.4 mg, 0.087 mmol) was added to the cooled reaction mixture and the mixture was stirred at 25 °C for 1 h. The reaction mixture was loaded onto Varian™ SCX column and washed with CH_3OH (20 mL). Product was eluted off using 2 N NH_3 in CH_3OH (6 mL) and concentrated to afford 1-(4-chlorobenzyl)-4-[{*N*-(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine as a colorless oil used without purification. Iodomethane (28 mg, 0.20 mmol) was added to a solution of 1-(4-chlorobenzyl)-4-[{*N*-(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine in CH_3CN (2.0 mL) and the reaction mixture was stirred at 70 °C for 4 h. The solvent was removed under reduced pressure to afford 1-(4-chlorobenzyl)-1-methyl-4-[{*N*-(3-

(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidinium iodide as a pale yellow oil (31.7 mg, 71%): The purity was determined by RPLC/MS (99%); ESI/MS m/e 482.1 (M^+, $C_{24}H_{28}ClF_3N_3O_2$).

Example 2026: Preparation of 1-{4-Chlorobenzyl}-4-[*N*-methyl-*N*-{*N*-(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine (Compound No. 520).

Formaldehyde (108 mg, 1.33 mmol, 37% wt solution in H_2O) was added to a solution of 1-(4-chlorobenzyl)-4-(aminomethyl)piperidine (318 mg, 1.33 mmol) and $NaBH_3CN$ (668 mg) in 10% CH_3COOH/CH_3OH (3 mL). The reaction mixture was stirred at 25 °C for 1 h. The reaction mixture was loaded on DOWEX™ 50Wx2 column (10 mL) and washed with CH_3OH (100 mL). Product was eluted off using 2 N NH_3 in CH_3OH (100 mL) and concentrated to afford 173 mg of crude 1-(4-chlorobenzyl)-4-{(methylamino)methyl}piperidine as a colorless oil used without purification.

EDCI (85 mg), 1-hydroxybenzotriazole hydrate (60 mg) were added to a solution of 1-(4-chlorobenzyl)-4-{(methylamino)methyl}piperidine (111 mg, 0.44 mmol) in CH_2Cl_2 (4 mL). The reaction mixture was stirred at 25 °C for 1 h and then washed with 2 N aqueous NaOH (2 mL X 2) and brine (1 mL). After filtration through PTFE membrane filter, the solvent was removed under reduced pressure to afford an yellow oil which was purified by preparative TLC (SiO_2, 5% CH_3OH/CH_2Cl_2) to give 1-(4-chlorobenzyl)-4-[*N*-methyl-*N*-{*N*-(3-(trifluoromethyl)benzoyl)glycyl}aminomethyl]piperidine (compound No. **520**) as a pale yellow oil (14.0 mg, 3.4%). The purity was determined by RPLC/MS (99%); ESI/MS m/e 482.1 (M^++H, $C_{24}H_{27}ClF_3N_3O_2$).

Reference Example 37: Preparation of 3-Aminohomopiperidine.

A solution of DL-α-amino-ε-caprolactam (2 g, 16 mmol) in THF (70 mL) was treated with 1 M BH_3-THF solution (80 mL) and heated to reflux for 3 h. 2 N aqueous HCl solution (50 mL) was added and the reaction was heated to reflux for an additional hour before cooling to 25 °C. The reaction was basicified (pH 10) by the addition of 4 N NaOH solution and extracted with EtOAc (3 x 200 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and concentrated to yield the desired material (990 mg, 54%) which was used without any further purification.

Reference Example 38: Preparation of 3-Amino-1-(4-chlorobenzyl)homopiperidine.

A solution of 3-aminohomopiperidine (1.71 g, 15 mmol) in CH_3CN (45 mL) was treated with *p*-chlorobenzyl chloride (463 mg, 2.9 mmol) and K_2CO_3 (828 g,

6 mmol) and heated to 70 °C for 9 h. The reaction mixture was cooled to 25 °C and concentrated to afford a yellow solid. The residue was partitioned between H_2O (5 mL) and EtOAc (50 mL), and extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4) and concentrated. The resulting yellow oil was purified by chromatography (SiO_2, 5-20% CH_3OH-CH_2Cl_2 gradient elution) to afford the desired product as a yellow oil (639 mg, 93%).

Example 2027: Preparation of 1-(4-Chlorobenzyl)-3-{(4-benzoylbutyryl)amino}homopiperidine (Compound No. 994).

A solution of 3-amino-1-(4-chlorobenzyl)homopiperidine (24 mg, 0.10 mmol) and 4-benzoylbutyric acid (1.2 equiv.) in CHCl3 (1 mL) was treated with EDCI (23 mg), HOBt (16.2 mg) and Et_3N (15.2 µL), and stirred at 25 °C for 16 h. The reaction mixture was diluted with CH_2Cl_2 (0.5 mL), washed with 2 N aqueous NaOH solution (2 x 0.75 mL), dried by filtration through a PTFE membrane and concentrated to afford 1-(4-chlorobenzyl)-3-{(4-benzoylbutyryl)amino}homopiperidine (compound No. **994**) (43 mg, 99%): The purity was determined by RPLC/MS (98%); ESI/MS m/e 413 (M^++H, $C_{24}H_{29}ClN_2O_2$).

Examples 2028-2042.

The compounds of this invention were synthesized pursuant to methods of Example 2027 using the corresponding reactant respectively. Chromatography (HPLC-C18), if needed, afforded the desired material as the TFA salt. The ESI/MS data and yields are summarized in Table 52.

Table 52

	Compound No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
Example 2028	943	C23 H25 Cl F3 N3 O2	468	6	28
Example 2029	944	C23 H28 Cl N3 O2	414	5	29
Example 2030	945	C22 H25 Cl N4 O4	445	6	30
Example 2031	946	C23 H27 Cl N4 O4	459	5	24
Example 2032	947	C25 H31 Cl N2 O4	459	4	20
Example 2033	948	C24 H29 Cl2 N3 O2	462	6	32
Example 2034	949	C25 H32 Cl N3 O2	442	6	31
Example 2035	988	C23 H25 Cl F3 N3 O2	468	45	92
Example 2036	989	C23 H28 Cl N3 O3	430	44	97
Example 2037	990	C22 H26 Cl N3 O2	400	41	99
Example 2038	991	C23 H27 Cl N2 O2	399	41	97

Example 2039	992	C25 H31 Cl N2 O4	459	47	98
Example 2040	993	C25 H31 Cl N2 O2	427	44	98
Example 2041	995	C25 H31 Cl N2 O3	443	44	95
Example 2042	996	C24 H31 Cl N4 O2	443	5*	11

*Yield of TFA salt.

Example 2043: Measurement of Inhibition of MIP-1α Binding to THP-1 Cells by Test Compounds.

Human monocytic leukemia cell line THP-1 was suspended in assay buffer (RPMI-1640 (Gibco-BRL Co.) containing 0.1% BSA and 25 mM HEPES adjusted to pH 7.4) to give a cell suspension of a concentration of 1 x 10^7 cells/mL. The test compound was diluted in the assay buffer and used as the test compound solution. Iodinated human MIP-1α (DuPont NEN Co.) was diluted in assay buffer to 250 nCi/mL and used as the labeled ligand solution. In a 96 well filter plate (Millipore Co.), 25 μL of test compound solution, 25 μL of labeled ligand solution and 50 μL of cell suspension were aliquoted into each well in this order, stirred (total reaction volume 100 μL), and incubated for one hour at 18 °C.

After the reaction, the reaction solution was filtered, and the filter was washed twice with 200 μL of cold PBS (200 μL of cold PBS was added and then filtered). The filter was air-dried and 25 μL of liquid scintillator was added into each well. The radioactivity retained by the cells on the filter were measured using TopCount (Packard Instrument Co.).

To calculate the ability of test compounds to inhibit binding of human MIP-1α to THP-1 cells, non-specific binding determined by adding 100 ng of unlabeled human MIP-1α (Peprotech Co.) in place of the test compound was subtracted, while the counts with no test compound added was taken as 100%.

$$\text{Inhibition (\%)} = \{1 - (A - B)/(C - B)\} \times 100$$

(A, counts with test compound added; B, counts with 100 ng of unlabeled human MIP-1α added; C, counts with [^{125}I]-labeled human MIP-1α added).

When inhibition by the cyclic amine derivative of this invention was measured, for example, the following compounds demonstrated 20-50%, 50%-80% and >80% inhibitory activity at 2 μM or 10 μM, respectively. These compounds are

20%-50% inhibition at 10 μM: Compound Nos. 29, 37, 41, 45, 46, 47, 50, 82, 85, 107, 120, 134, 214, 217, 218, 220, 222, 225, 226, 227, 228, 229, 230, 231, 233, 234, 236, 237, 238, 333, 334, 335, 336, 338, 340, 342, 347, 348, 349, 350, 352, 357, 359, 361, 366, 372, 374, 375, 376, 380, 382, 383, 385, 470, 471, 472, 473, 474, 483, 484, 488, 489, 491, 497, 499, 500, 502, 506, 508, 510, 514, 515, 518, 524, 543, 553, 554, 555, 556, 563, 571, 575, 576, 578, 579, 580, 583, 586, 587, 588, 590, 591, 592, 595, 596, 598, 603, 610, 611, 612, 614, 624, 625, 626, 629, 635, 638, 639, 640, 641, 642, 643, 644, 646, 647, 648, 649, 652, 653, 658, 659, 660, 665, 666, 669, 671, 675, 677, 679, 681, 682, 684, 691, 695, 696, 700, 702, 704, 706, 711, 712, 714, 717, 721, 723, 724, 726, 727, 728, 729, 731, 737, 739, 740, 741, 742, 744, 746, 765, 767, 772, 773, 774, 775, 776, 780, 781, 785, 786, 787, 788, 790, 791, 792, 793, 795, 796, 797, 798, 805, 806, 807, 810, 813, 820, 821, 822, 824, 825, 827, 829, 830, 833, 834, 837, 838, 844, 853, 855, 873, 877, 878, 880, 882, 887, 888, 891, 894, 901, 903, 904, 905, 911, 929, 932, 933, 935, 938, 940, 948, 993, 996, 1006, 1018, 1026, 1028, 1035, 1048, 1053, 1054, 1055, 1056, 1068, 1070, 1071, 1072, 1073, 1075, 1076, 1081, 1763, 1764.

50%-80% inhibition at 10 μM: Compound Nos. 1, 2, 3, 4, 7, 13, 22, 23, 24, 25, 27, 31, 32, 38, 48, 83, 119, 121, 123, 131, 215, 216, 221, 235, 337, 351, 354, 358, 362, 363, 365, 367, 368, 369, 373, 378, 381, 384, 458, 459, 463, 465, 466, 467, 468, 478, 479, 480, 482, 485, 486, 487, 492, 493, 494, 495, 496, 498, 501, 503, 504, 507, 511, 512, 513, 520, 523, 527, 529, 530, 531, 532, 533, 534, 535, 536, 537, 538, 539, 540, 541, 542, 545, 546, 547, 548, 549, 550, 551, 552, 558, 559, 560, 561, 562, 565, 567, 568, 569, 570, 572, 573, 574, 577, 581, 582, 594, 597, 599, 600, 602, 604, 606, 607, 608, 609, 613, 615, 616, 618, 619, 620, 621, 628, 630, 631, 632, 633, 634, 636, 637, 645, 651, 654, 655, 657, 661, 662, 664, 673, 674, 676, 678, 680, 683, 685, 687, 688, 689, 693, 703, 705, 707, 708, 709, 710, 713, 716, 718, 719, 720, 725, 730, 732, 733, 734, 735, 736, 749, 750, 751, 752, 753, 754, 756, 758, 760, 762, 763, 764, 766, 768, 769, 770, 771, 777, 778, 779, 784, 794, 799, 800, 802, 804, 808, 809, 811, 812, 815, 816, 819, 828, 831, 832, 835, 836, 839, 840, 845, 846, 847, 848, 850, 851, 854, 857, 858, 859, 860, 861, 862, 863, 865, 866, 867, 868, 872, 874, 876, 886, 899, 910, 942, 998, 1004, 1005, 1007, 1013, 1015, 1016, 1017, 1019, 1020, 1021, 1022, 1024, 1030, 1037, 1042, 1043, 1044, 1045, 1046, 1047, 1049, 1050, 1052, 1059, 1060, 1061, 1067, 1069, 1074, 1078, 1079, 1080, 1766.

>80% inhibition at 10 μM: Compound Nos. 461, 464, 469, 481, 490, 505, 509, 521, 526, 528, 544, 564, 566, 601, 605, 617, 622, 623, 627, 650, 656, 663, 668, 672, 686, 690, 692, 694, 715, 743, 747, 748, 755, 757, 759, 761, 782, 783, 803, 814, 817, 818, 826, 849, 856, 864, 869, 870, 871, 999, 1000, 1001, 1002, 1003, 1008,

1009, 1010, 1011, 1012, 1023, 1029, 1031, 1032, 1033, 1034, 1036, 1038, 1039, 1040, 1041, 1051, 1057, 1058, 1062, 1063, 1064, 1065, 1066, 1082, 1083.

20%-50% inhibition at 2 μM: Compound Nos. **1042, 1043, 1244, 1245, 1416, 1435, 1436, 1438, 1441, 1480, 1570, 1583, 1584, 1589, 1590, 1594, 1595, 1601, 1660, 1672, 1687, 1724, 1779, 1780, 1787, 1795, 1796, 1798, 1799, 1802, 1893, 1894, 1898, 1900, 1915, 1919, 1920, 2092, 2096, 2098, 2100.**

50%-80% inhibition at 2 μM: Compound Nos. **1190, 1414, 1600, 2091, 2094, 2095.**

>80% inhibition at 2 μM: Compound Nos. **2093, 2097, 2099, 2103, 2104.**

Example 2044: Measurement of Inhibition of MCP-1 Binding to THP-1 Cells.

1. Construction of recombinant baculovirus carrying the human MCP-1 gene

Based on the previously published human MCP-1 gene sequence (for example T. Yoshimura et al., FEBS Lett., 1989, 244, 487-493), two synthetic DNA primers (5'-CACTCTAGACTCCAGCATGA-3' and 5'-TAGCTGCAGATTCTTGGGTTG-3') flanked by restriction enzyme sites were used to amplify a DNA fragment from cDNA derived from human endothelial cells (purchased from Kurabow Co.); the amplified fragment was cut with the restriction enzymes (PstI and XbaI), ligated into a transfer vector pVL1393 (Invitrogen Co.), and the resulting vector was co-transfected along with infectious baculovirus into Sf-9 insect cells and the supernatant was plaque assayed to yield human MCP-1 gene baculovirus recombinant.

2. Synthesis of [^{125}I]-labeled human MCP-1 expressed in baculovirus

Using the method of K. Ishii et al. (Biochem Biophys Research Communications, 1995, 206, 955-961), 5 x 10^6 Sf-6 insect cells was infected with 5 x 10^7 PFU (plaque forming units) of the above human MCP-1 recombinant baculovirus and cultured for 7 days in Ex-Cell 401 medium. The culture supernatant was affinity purified using a heparin Sepharose column (Pharmacia Co.) and then further purified using reverse phase HPLC (Vydac C18 column) to prepare purified human MCP-1. The purified human MCP-1 was protein labeled by Amersham Co. using the Bolton Hunter method to yield [^{125}I]-labeled baculovirus expressed human MCP-1 (specific activity 2000 Ci/mmol).

3-1. Measurement of inhibition of binding of [^{125}I]-labeled baculovirus expressed human MCP-1 to THP-1 cells (Method 1)

Human monocytic leukemia cell line THP-1 was suspended in assay buffer

(RPMI-1640 (Gibco-BRL Co.) containing 0.1% BSA and 25 mM HEPES adjusted to pH 7.4) to give a cell suspension of a concentration of 1 x 10^7 cells/mL. The test compound was diluted in the assay buffer and used as the test compound solution. [^{125}I]-labeled human MCP-1 described above was diluted in assay buffer to 1 mCi/mL and used as the labeled ligand solution. In a 96 well filter plate (Millipore Co.), 25 μL of test compound solution, 25 μL of labeled ligand solution and 50 μL of cell suspension were aliquoted into each well in this order, stirred (total reaction volume 100 μL), and incubated for one hour at 18 °C.

After the reaction, the reaction solution was filtered, and the filter was washed twice with 200 μL of cold PBS (200 μL of cold PBS was added and then filtered). The filter was air-dried and 25 μL of liquid scintillator was added into each well. The radioactivity retained by the cells on the filter were measured using TopCount (Packard Instrument Co.).

To calculate the ability of test compound to inhibit binding of human MCP-1 to THP-1 cells, non-specific binding determined by adding 100 ng of unlabeled human MCP-1 in place of the test compound was subtracted, while the counts with no test compound added was taken as 100%.

$$\text{Inhibition (\%)} = \{1 - (A - B)/(C - B)\} \times 100$$

(A, counts with test compound added; B, counts with 100 ng of unlabeled human MCP-1 added; C, counts with [^{125}I]-labeled human MCP-1 added).

When inhibition by the cyclic amine derivative of this invention was measured, for example, the following compounds demonstrated 20%-50%, 50%-80% and >80% inhibitory activity at 1 μM, 10 μM or 100 μM, respectively. These compounds are

20%-50% inhibition at 100 μM: Compound Nos. **3, 6, 11, 15, 16, 19, 28, 44, 88, 92, 94, 104, 111, 112, 124, 125, 133, 219, 220, 224, 228, 236, 338, 343, 346, 347, 348, 349, 362, 363, 367, 368, 371, 373, 381, 618, 847, 849, 850, 866, 867, 869, 870, 871, 872, 873.**

50%-80% inhibition at 100 μM: Compound Nos. **1, 8, 10, 12, 18, 21, 26, 30, 33, 35, 39, 84, 89, 90, 91, 96, 97, 98, 99, 100, 101, 103, 106, 108, 109, 110, 116, 122, 126, 216, 218, 221, 225, 226, 231, 330, 332, 333, 334, 337, 341, 342, 350, 352, 354, 356, 359, 360, 361, 364, 366, 374, 375, 379, 382, 462, 463, 464, 557, 686, 840, 841, 842, 843, 844, 845, 846, 848, 862, 863, 864, 865, 868.**

>80% inhibition at 100 μM: Compound Nos. 2, 4, 5, 7, 13, 14, 17, 20, 22, 23, 24, 25, 27, 29, 31, 32, 34, 36, 38, 40, 41, 42, 43, 45, 46, 47, 48, 49, 50, 83, 85, 86, 95, 102, 105, 107, 113, 114, 115, 119, 120, 121, 123, 127, 128, 129, 130, 131, 132, 134, 214, 215, 217, 227, 237, 238, 331, 335, 336, 339, 340, 345, 351, 355, 357, 358, 383, 458, 459, 460, 466, 558, 851, 852, 861, 874.

20%-50% inhibition at 10 μM: Compound Nos. 12, 18, 30, 34, 40, 42, 43, 51, 52, 53, 54, 55, 56, 57, 59, 60, 64, 66, 75, 76, 77, 78, 79, 82, 89, 90, 97, 98, 102, 103, 116, 127, 128, 129, 130, 132, 135, 136, 140, 141, 144, 156, 157, 159, 160, 161, 162, 163, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 178, 179, 190, 191, 192, 195, 197, 200, 202, 203, 204, 205, 208, 233, 234, 235, 239, 240, 241, 242, 243, 245, 247, 249, 250, 255, 263, 264, 269, 274, 278, 279, 282, 306, 316, 317, 323, 324, 380, 404, 409, 433, 446, 448, 449, 451, 470, 471, 473, 476, 479, 486, 488, 489, 497, 498, 499, 501, 504, 507, 508, 509, 510, 512, 514, 516, 519, 527, 530, 532, 542, 545, 560, 563, 564, 565, 566, 568, 569, 572, 573, 574, 575, 578, 583, 584, 586, 587, 589, 590, 599, 600, 601, 603, 606, 612, 613, 620, 621, 622, 624, 625, 627, 629, 630, 632, 634, 636, 637, 640, 641, 642, 643, 644, 645, 646, 647, 648, 649, 658, 678, 682, 687, 692, 694, 764, 775, 856, 857, 860, 881, 882, 883, 884, 890, 892, 899, 900, 903, 905, 907, 908, 911, 912, 916, 917, 921, 922, 923, 925, 927, 931, 932, 935, 939, 940, 968, 986, 1039, 1041, 1045, 1047, 1062, 1063, 1083.

50%-80% inhibition at 10 μM: Compound Nos. 7, 32, 36, 61, 62, 63, 65, 67, 69, 70, 71, 72, 73, 74, 81, 91, 105, 114, 121, 123, 134, 137, 138, 139, 146, 147, 148, 149, 151, 154, 165, 177, 232, 244, 248, 251, 252, 253, 256, 259, 261, 266, 267, 276, 286, 292, 293, 295, 301, 305, 307, 310, 314, 315, 320, 322, 328, 434, 435, 436, 437, 439, 440, 443, 447, 450, 452, 453, 454, 455, 456, 468, 469, 472, 474, 475, 477, 478, 480, 481, 482, 483, 485, 490, 493, 494, 500, 505, 511, 517, 520, 529, 534, 540, 543, 544, 548, 555, 556, 561, 562, 570, 576, 579, 611, 617, 853, 854, 855, 858, 859, 875, 877, 879, 880, 885, 886, 887, 888, 891, 894, 895, 904, 906, 909, 910, 913, 914, 918, 928, 930, 933, 937, 938, 945, 970, 1040, 1044, 1046.

>80% inhibition at 10 μM: Compound Nos. 31, 45, 46, 48, 58, 68, 80, 83, 113, 115, 142, 143, 145, 150, 152, 265, 268, 272, 275, 283, 285, 287, 288, 290, 291, 294, 296, 297, 302, 308, 309, 313, 321, 325, 326, 358, 438, 441, 442, 444, 445, 457, 466, 467, 484, 487, 491, 492, 495, 496, 503, 518, 537, 538, 547, 554, 876, 878, 919, 929, 943.

20%-50% inhibition at 1 μM: Compound Nos. 1118, 1121, 1136, 1143, 1146, 1158, 1159, 1167, 1170, 1359, 1361, 1362, 1363.

50%-80% inhibition at 1 μM: Compound Nos. 1133, 1134, 1137, 1141, 1156, 1161,

1162, 1163, 1164, 1166.

>80% inhibition at 1 μM: Compound No. **1147.**

3-2. Measurement of inhibition of binding of $[^{125}I]$-labeled baculovirus expressed human MCP-1 to THP-1 cells (Method 2)

Human monocytic leukemia cell line THP-1 was suspended in assay buffer (50 mM HEPES, pH 7.4, 1.0 mM $CaCl_2$, 5.0 mM $MgCl_2$, 0.5% BSA) to give a cell suspension of a concentration of 1×10^7 cells/mL. The test compound was diluted in the assay buffer and used as the test compound solution. $[^{125}I]$-labeled human MCP-1 described above was diluted in assay buffer to 1 mCi/mL and used as the labeled ligand solution. In a 96 well filter plate (Millipore Co.), 25 μL of test compound solution, 25 μL of labeled ligand solution and 50 μL of cell suspension were aliquoted into each well in this order, stirred (total reaction volume 100 μL), and incubated for one hour at 18 °C.

After the reaction, the reaction solution was filtered, and the filter was washed twice with 200 μL of cold PBS (200 μL of cold PBS was added and then filtered). The filter was air-dried and 25 μL of liquid scintillator was added into each well. The radioactivity retained by the cells on the filter were measured using TopCount (Packard Instrument Co.).

To calculate the ability of test compound to inhibit binding of human MCP-1 to THP-1 cells, non-specific binding determined by adding 100 ng of unlabeled human MCP-1 in place of the test compound was subtracted, while the counts with no test compound added was taken as 100%.

$$\text{Inhibition } (\%) = \{1 - (A - B)/(C - B)\} \times 100$$

(A, counts with test compound added; B, counts with 100 ng of unlabeled human MCP-1 added; C, counts with $[^{125}I]$-labeled human MCP-1 added).

When inhibition by the cyclic amine derivative of this invention was measured, for example, the following compounds demonstrated 20%-50%, 50%-80% and >80% inhibitory activity at 0.2 μM, 1 μM or 10 μM, respectively. These compounds are

20%-50% inhibition at 10 μM: Compound No. **1560.**

50%-80% inhibition at 10 μM: Compound No. **1550.**

>80% inhibition at 10 μM: Compound Nos. 541, 1042, 1043, 1559.

20%-50% inhibition at 1 μM: Compound Nos. 1098, 1100, 1101, 1104, 1105, 1109, 1110, 1116, 1174, 1175, 1176, 1178, 1187, 1188, 1189, 1197, 1198, 1199, 1200, 1201, 1202, 1209, 1210, 1211, 1212, 1222, 1225, 1229, 1230, 1237, 1238, 1243, 1250, 1259, 1261, 1265, 1266, 1272, 1277, 1282, 1294, 1299, 1302, 1307, 1315, 1318, 1319, 1320, 1329, 1330, 1335, 1336, 1337, 1343, 1344, 1353, 1355, 1356, 1357, 1358, 1368, 1372, 1385, 1386, 1392, 1400, 1413, 1422, 1423, 1425, 1426, 1429, 1430, 1432, 1437, 1440, 1445, 1446, 1447, 1448, 1450, 1452, 1453, 1455, 1458, 1459, 1461, 1463, 1464, 1466, 1468, 1469, 1470, 1471, 1474, 1479, 1482, 1485, 1507, 1508, 1510, 1511, 1512, 1513, 1514, 1515, 1516, 1518, 1519, 1521, 1522, 1524, 1535, 1538, 1540, 1542, 1544, 1571, 1573, 1574, 1575, 1576, 1577, 1578, 1579, 1580, 1581, 1582, 1585, 1587, 1598, 1602, 1603, 1604, 1609, 1611, 1612, 1613, 1614, 1615, 1616, 1617, 1618, 1622, 1627, 1630, 1643, 1646, 1662, 1669, 1716, 1717, 1723, 1728, 1731, 1733, 1736, 1739, 1740, 1747, 1750, 1755, 1757, 1758, 1759, 1760, 1761, 1762, 1769, 1770, 1771, 1772, 1773, 1774, 1777, 1783, 1784, 1785, 1791, 1793, 1904, 1911, 1917, 2057, 2061, 2063, 2064, 2065, 2066, 2067, 2068, 2069, 2071, 2072, 2073, 2074, 2075, 2076, 2080, 2081, 2082, 2110, 2112, 2123, 2130, 2131, 2139.

50%-80% inhibition at 1 μM: Compound Nos. 37, 298, 318, 1084, 1091, 1103, 1106, 1108, 1111, 1113, 1114, 1115, 1138, 1142, 1165, 1179, 1190, 1192, 1193, 1195, 1196, 1204, 1205, 1206, 1207, 1208, 1245, 1246, 1255, 1257, 1258, 1262, 1263, 1293, 1300, 1342, 1351, 1352, 1354, 1370, 1371, 1373, 1375, 1377, 1378, 1380, 1381, 1383, 1384, 1391, 1411, 1412, 1414, 1417, 1418, 1419, 1421, 1424, 1431, 1436, 1439, 1449, 1454, 1456, 1457, 1460, 1462, 1472, 1473, 1487, 1502, 1504, 1506, 1517, 1525, 1526, 1527, 1529, 1530, 1531, 1532, 1533, 1534, 1536, 1537, 1539, 1541, 1545, 1593, 1600, 1601, 1606, 1608, 1619, 1620, 1621, 1623, 1624, 1625, 1626, 1628, 1629, 1645, 1650, 1654, 1658, 1663, 1664, 1665, 1670, 1671, 1672, 1673, 1675, 1678, 1679, 1681, 1684, 1687, 1688, 1689, 1690, 1711, 1712, 1714, 1718, 1722, 1725, 1726, 1727, 1729, 1730, 1732, 1734, 1735, 1737, 1741, 1742, 1743, 1744, 1745, 1746, 1748, 1751, 1753, 1754, 1756, 1779, 1781, 1782, 1786, 1788, 1789, 1790, 1792, 1795, 1797, 1798, 1800, 1801, 1804, 1848, 1862, 1883, 1885, 1886, 1887, 1889, 1893, 1894, 1903, 1905, 1910, 1912, 1913, 1914, 1918, 1922, 1976, 1985, 2027, 2035, 2062, 2083, 2084, 2088, 2089, 2090, 2111, 2124, 2125, 2126, 2135.

>80% inhibition at 1 μM: Compound Nos. 299, 311, 312, 329, 1042, 1043, 1085, 1119, 1191, 1203, 1220, 1228, 1236, 1244, 1256, 1288, 1295, 1308, 1310, 1376, 1382, 1393, 1395, 1415, 1416, 1420, 1435, 1438, 1441, 1480, 1481, 1570, 1583, 1584, 1589, 1590, 1594, 1595, 1607, 1634, 1660, 1661, 1666, 1668, 1695, 1696,

1697, 1698, 1699, 1701, 1702, 1703, 1704, 1705, 1706, 1707, 1708, 1709, 1713, 1724, 1749, 1752, 1775, 1776, 1778, 1780, 1787, 1794, 1796, 1799, 1802, 1803, 1841, 1869, 1870, 1871, 1872, 1876, 1877, 1892, 1896, 1897, 1898, 1899, 1900, 1901, 1902, 1906, 1907, 1908, 1909, 1915, 1916, 1919, 1920, 1921, 2085, 2086, 2087, 2113, 2114, 2118, 2119, 2120, 2121, 2122, 2127, 2128, 2129, 2132, 2133, 2136, 2137, 2138, 2159, 2161, 2162, 2187, 2189, 2193.

20%-50% inhibition at 0.2 μM: Compound Nos. **1680, 1682, 1686, 1691, 1694, 1700, 1805, 1810, 1811, 1812, 1813, 1815, 1816, 1817, 1818, 1819, 1820, 1824, 1825, 1826, 1827, 1828, 1832, 1833, 1834, 1835, 1836, 1839, 1840, 1842, 1843, 1851, 1852, 1853, 1854, 1855, 1856, 1858, 1859, 1860, 1863, 1864, 1865, 1866, 1868, 1874, 1878, 1879, 1880, 1888, 1890, 1891, 1895, 1926, 1927, 1928, 1929, 1930, 1934, 1935, 1937, 1945, 1946, 1951, 1952, 1953, 1954, 1959, 1960, 1961, 1962, 1966, 1969, 1970, 1971, 1972, 1973, 1977, 1978, 1979, 1980, 1981, 1985, 2014, 2027, 2028, 2033, 2035, 2039, 2040, 2041, 2042, 2044, 2045, 2046.**

50%-80% inhibition at 0.2 μM: Compound Nos. **1677, 1678, 1679, 1681, 1687, 1688, 1689, 1690, 1695, 1697, 1808, 1809, 1841, 1848, 1861, 1862, 1869, 1870, 1871, 1872, 1873, 1876, 1877, 1883, 1884, 1885, 1886, 1887, 1889, 1893, 1894, 1976.**

>80% inhibition at 0.2 μM: Compound No. **1696, 1892.**

Example 2045: Measurement of Inhibition of Binding of [^{125}I]-Labeled Human MCP-1 to Cells Expressing the MCP-1 Receptor.

1. Derivation of cells expressing the MCP-1 receptor

cDNA fragment containing the MCP-1 receptor reported by S. Yamagami et al., Biochemical Biophysical Research Communications 1994, 202, 1156-1162) was cloned into the expression plasmid pCEP4 (Invitrogen Co.) at the NotI site, and the plasmid obtained was transfected into the human kidney epithelial cell line 293-EBNA using the Lipofectamine reagent (Gibco-BRL Co.). The cells were cultured in the presence of the selective agent (Hygromycin), and a stably expressing transfectant line was obtained. The expression of the receptor was confirmed by binding of [^{125}I]-labeled human MCP-1.

2. Measurement of inhibition of binding of [^{125}I]-labeled baculovirus expressed human MCP-1 to the MCP-1 receptor expressing cells

The MCP-1 receptor expressing cells on tissue culture dishes were scraped using a cell scraper and suspended in assay buffer (D-MEM(Gibco-BRL Co.) containing 0.1% BSA and 25 mM HEPES adjusted to pH 7.4) to give a cell suspension of a concentration of 6×10^6 cells/mL. The test compound was diluted in the assay buffer. The remainder of the procedure was as described in Example 2044.

When the inhibition by some typical compounds of the present invention was measured, the inhibitory activities were substantially the same as those in Example 2044, respectively.

Example 2046: Measurement of Inhibition of Cell Chemotaxis.

In order to determine the inhibition of cell chemotaxis by the compounds of this invention, we measured cell chemotaxis caused by monocyte chemotactic factor MCP-1 using the human monocytic leukemia cell line THP-1 as the chemotactic cell according to the method of Fall et al. (J. Immunol. Methods, 190, 33, 239-247). 2×10^6 cells/mL of THP-1 cells (suspended in RPMI-1640 (Flow Laboratories Co.) + 10% FCS) was placed in the upper chamber (200 μL) of a 96 well micro-chemotaxis chamber (Neuroprobe, registered tradename), and human recombinant MCP-1 in a same solution (Peprotech Co.) at a final concentration of 20 ng/mL was placed in the lower chamber, with a polycarbonate filter (PVP-free, Neuroprobe; registered tradename) placed between the two chambers. These were incubated at 37 °C for 2 hr in 5% CO_2.

The filter was removed, and the cells which had migrated to the underside of the filter was fixed, stained using Diff Quick (Kokusai Shiyaku Co.) and then quantitated using a plate reader (Molecular Device Co.) at a wavelength of 550 nm to determine the index of cell migration as a mean of 3 wells. In addition, test compounds were placed in the upper and lower chambers along with THP-1 and MCP-1, respectively, and the inhibition of cell migration (inhibition IC_{50} (μM)) was determined. Inhibition was defined as {(cells migration induced MCP-1 with no test compound in the upper and lower chambers) - (cells migration with no MCP-1 added in the lower chamber) = 100%}, and the concentration of the test compound which gave 50% inhibition was designated IC_{50}.

When inhibition by the cyclic amine derivative of this invention was measured, for example, the 50% inhibition concentration (IC_{50}) for the following compounds were IC_{50} < 0.1 μM.

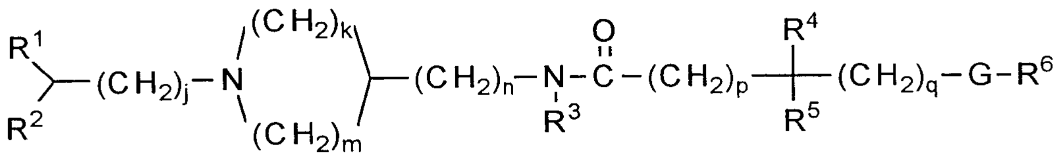
IC_{50} < 0.1 μM: Compound Nos. **4, 37, 298, 299, 311, 312, 318, 329, 461, 886, 909, 1042, 1043, 1085, 1119, 1138, 1142, 1165, 1179, 1191, 1203, 1205, 1220, 1228, 1236, 1244, 1245, 1256, 1288, 1293, 1295, 1308, 1310, 1352, 1376, 1382, 1393, 1395, 1416, 1420, 1435, 1436, 1438, 1441, 1480, 1531, 1532, 1570, 1583, 1584, 1589, 1590, 1594, 1595, 1600, 1601, 1607, 1660, 1661, 1664, 1666, 1668, 1698, 1699, 1701, 1702, 1703, 1704, 1706, 1707, 1708, 1709, 1713, 1775, 1776, 1778, 1779, 1787, 1794, 1796, 1799, 1802, 1803, 1896, 1898, 1899, 1900, 1901, 1902,**

1906, 1907, 1908, 1909, 1915, 1916, 1919, 1920, 1921, 2087, 2114, 2128, 2129, 2132, 2137, 2141, 2144, 2157, 2158, 2189.

Claims

What is claimed is:

1. A compound of the formula (I) below:



(I)

, a pharmaceutically acceptable acid addition salt thereof or a pharmaceutically acceptable C_1-C_6 alkyl addition salt thereof,

wherein R^1 is a phenyl group, a C_3-C_8 cycloalkyl group, or an aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof, in which the phenyl or aromatic heterocyclic group may be condensed with a benzene ring or an aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof, to form a condensed ring, and the phenyl group, C_3-C_8 cycloalkyl group, aromatic heterocyclic group, or condensed ring may be substituted with one or more of a halogen atom, a hydroxy group, a cyano group, a nitro group, a carboxy group, a carbamoyl group, a C_1-C_6 alkyl group, a C_3-C_8 cycloalkyl group, a C_2-C_6 alkenyl group, a C_1-C_6 alkoxy group, a C_1-C_6 alkylthio group, a C_3-C_5 alkylene group, a C_2-C_4 alkylenoxy group, a C_1-C_3 alkylenedioxy group, a phenyl group, a phenoxy group, a phenylthio group, a benzyl group, a benzyloxy group, a benzoylamino group, a C_2-C_7 alkanoyl group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 alkanoyloxy group, a C_2-C_7 alkanoylamino group, a C_2-C_7 *N*-alkylcarbamoyl group, a C_4-C_9 *N*-cycloalkylcarbamoyl group, a C_1-C_6 alkylsulfonyl group, a C_3-C_8 (alkoxycarbonyl)methyl group, a *N*-phenylcarbamoyl group, a piperidinocarbonyl group, a morpholinocarbonyl group, a 1-pyrrolidinylcarbonyl group, a divalent group represented by the formula: -NH(C=O)O-, a divalent group represented by the formula: -NH(C=S)O-, an amino group, a mono(C_1-C_6 alkyl)amino group, or a di(C_1-C_6 alkyl)amino group, wherein the substituent for the phenyl group, C_3-C_8 cycloalkyl group, aromatic heterocyclic group, or condensed ring is optionally substituted with one or more of a halogen atom, a hydroxy group, an amino group, a trifluoromethyl group, a C_1-C_6 alkyl group, or a C_1-C_6 alkoxy group;

R^2 is a hydrogen atom, a C_1-C_6 alkyl group, a C_2-C_7 alkoxycarbonyl group, a hydroxy group, or a phenyl group, in which the C_1-C_6 alkyl or phenyl group may

be substituted with one or more of a halogen atom, a hydroxy group, a C_1-C_6 alkyl group, or a C_1-C_6 alkoxy group, and when j = 0, R^2 is not a hydroxy group;

j represents an integer of 0-2;

k represents an integer of 0-2;

m represents an integer of 2-4;

n represents 0 or 1;

R^3 is a hydrogen atom or a C_1-C_6 alkyl group optionally substituted with one or two phenyl groups each of which may be substituted with one or more of a halogen atom, a hydroxy group, a C_1-C_6 alkyl group, or a C_1-C_6 alkoxy group;

R^4 and R^5 are the same or different from each other and are a hydrogen atom, a hydroxy group, a phenyl group, or a C_1-C_6 alkyl group, in which the C_1-C_6 alkyl group is optionally substituted with one or more of a halogen atom, a hydroxy group, a cyano group, a nitro group, a carboxy group, a carbamoyl group, a mercapto group, a guanidino group, a C_3-C_8 cycloalkyl group, a C_1-C_6 alkoxy group, a C_1-C_6 alkylthio group, a phenyl group optionally substituted with one or more of a halogen atom, a hydroxy group, a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, or a benzyloxy group, a phenoxy group, a benzyloxy group, a benzyloxycarbonyl group, a C_2-C_7 alkanoyl group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 alkanoyloxy group, a C_2-C_7 alkanoylamino group, a C_2-C_7 *N*-alkylcarbamoyl group, a C_1-C_6 alkylsulfonyl group, an amino group, a mono(C_1-C_6 alkyl)amino group, a di(C_1-C_6 alkyl)amino group, or an aromatic heterocyclic group having 1-3 of heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof and optionally condensed with benzene ring, or R^4 and R^5 taken together form a 3 to 6 membered cyclic hydrocarbon;

p represents 0 or 1;

q represents 0 or 1;

G is a group represented by -CO-, $-SO_2-$, -CO-O-, $-NR^7-CO-$, $-CO-NR^7-$, -NH-CO-NH-, -NH-CS-NH-, $-NR^7-SO_2-$, $-SO_2-NR^7-$, -NH-CO-O-, or -O-CO-NH-, wherein R^7 is a hydrogen atom or a C_1-C_6 alkyl group, or R^7 taken together with R^5 represents C_2-C_5 alkylene group;

R^6 is a phenyl group, a C_3-C_8 cycloalkyl group, a C_3-C_8 cycloalkenyl group, a benzyl group, or an aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof, in which the phenyl, benzyl, or aromatic heterocyclic group may be condensed with a benzene ring or an aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof, to form a condensed

ring, and the phenyl group, C_3-C_8 cycloalkyl group, C_3-C_8 cycloalkenyl group, benzyl group, aromatic heterocyclic group, or condensed ring may be substituted with one or more of a halogen atom, a hydroxy group, a mercapto group, a cyano group, a nitro group, a thiocyanato group, a carboxy group, a carbamoyl group, a trifluoromethyl group, a C_1-C_6 alkyl group, a C_3-C_6 cycloalkyl group, a C_2-C_6 alkenyl group, a C_1-C_6 alkoxy group, a C_3-C_8 cycloalkyloxy group, a C_1-C_6 alkylthio group, a C_1-C_3 alkylenedioxy group, a phenyl group, a phenoxy group, a phenylamino group, a benzyl group, a benzoyl group, a phenylsulfinyl group, a phenylsulfonyl group, a 3-phenylureido group, a C_2-C_7 alkanoyl group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 alkanoyloxy group, a C_2-C_7 alkanoylamino group, a C_2-C_7 *N*-alkylcarbamoyl group, a C_1-C_6 alkylsulfonyl group, a phenylcarbamoyl group, a *N,N*-di(C_1-C_6 alkyl)sulfamoyl group, an amino group, a mono(C_1-C_6 alkyl)amino group, a di(C_1-C_6 alkyl)amino group, a benzylamino group, a C_2-C_7 (alkoxycarbonyl)amino group, a C_1-C_6 (alkylsulfonyl)amino group, or a bis(C_1-C_6 alkylsulfonyl)amino group, wherein the substituent for the phenyl group, C_3-C_8 cycloalkyl group, C_3-C_8 cycloalkenyl group, benzyl group, aromatic heterocyclic group, or condensed ring is optionally substituted with one or more of a halogen atom, a cyano group, a hydroxy group, an amino group, trifluoromethyl group, a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a C_1-C_6 alkylthio group, a mono(C_1-C_6 alkyl)amino group, or a di(C_1-C_6 alkyl)amino group.

2. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable C_1-C_6 alkyl addition salt as set forth in claim 1, wherein k = 1 and m = 2 in the above formula (I).

3. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable C_1-C_6 alkyl addition salt as set forth in claim 2, wherein n = 0 in the above formula (I).

4. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable C_1-C_6 alkyl addition salt as set forth in claim 1, wherein k = 0, m = 3 and n = 1 in the above formula (I).

5. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable C_1-C_6 alkyl addition salt as set forth in claim 1, wherein k = 1 and m = 3 in the above formula (I).

6. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable C_1-C_6 alkyl addition salt as set forth in claim 1, wherein $k = 2$ and $m = 2$ in the above formula (I).

7. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable C_1-C_6 alkyl addition salt as set forth in claim 6, wherein $n = 1$ in the above formula (I).

8. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable C_1-C_6 alkyl addition salt as set forth in claim 1, wherein $k = 1$ and $m = 4$ in the above formula (I).

9. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable C_1-C_6 alkyl addition salt as set forth in claim 1, wherein $j = 0$ in the above formula(I).

10. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable C_1-C_6 alkyl addition salt as set forth in claim 1, wherein $p = 0$, $q = 0$ and G is a group represented by $-NR^7-CO-$ in the above formula (I).

11. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable C_1-C_6 alkyl addition salt as set forth in claim 1, wherein R^2 is a hydrogen atom, R^3 is a hydrogen atom and R^7 is a hydrogen atom in the above formula (I).

12. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable C_1-C_6 alkyl addition salt as set forth in claim 1, wherein the substituent for the phenyl group, C_3-C_8 cycloalkyl group, aromatic heterocyclic group, or condensed ring in R^1 is one or more of a halogen atom, a hydroxy group, a C_1-C_6 alkyl group, a C_2-C_6 alkenyl group, a C_1-C_6 alkoxy group, a C_1-C_6 alkylthio group, a C_2-C_4 alkylenoxy group, a methylenedioxy group, a *N*-phenylcarbamoyl group, an amino group, a mono(C_1-C_6 alkyl)amino group, or a di(C_1-C_6 alkyl)amino group in the above formula (I).

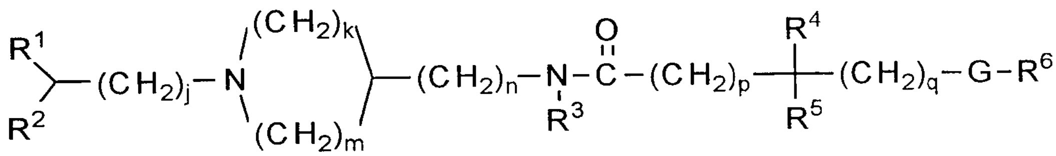
13. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable C_1-C_6 alkyl addition salt as set forth in claim 1,

wherein the substituent for the phenyl group, C_3-C_8 cycloalkyl group, C_3-C_8 cycloalkenyl group, benzyl group, aromatic heterocyclic group, or condensed ring in R^6 is one or more of a halogen atom, a nitro group, a trifluoromethyl group, a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a phenylsulfonyl group, a C_2-C_7 alkanoylamino group, or an amino group in the above formula (I).

14. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable C_1-C_6 alkyl addition salt as set forth in claim 1, wherein R^1 is a phenyl group or an isoxazolyl group in the above formula (I).

15. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable C_1-C_6 alkyl addition salt as set forth in claim 1, wherein R^6 is a phenyl group, a furyl group, or a thienyl group in the above formula (I).

16. A method of inhibiting the binding of a chemokine to the receptor of a target cell and/or its action on a target cell using a pharmaceutical preparation containing a therapeutically effective amount of a compound represented by the formula (I) below:



(I)

, a pharmaceutically acceptable acid addition salt thereof or a pharmaceutically acceptable C_1-C_6 alkyl addition salt thereof,

wherein R^1 is a phenyl group, a C_3-C_8 cycloalkyl group, or an aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof, in which the phenyl or aromatic heterocyclic group may be condensed with a benzene ring or an aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof, to form a condensed ring, and the phenyl group, C_3-C_8 cycloalkyl group, aromatic heterocyclic group, or condensed ring may be substituted with one or more of a halogen atom, a hydroxy group, a cyano group, a nitro group, a carboxy group, a carbamoyl group, a C_1-C_6 alkyl group, a C_3-C_8 cycloalkyl group, a C_2-C_6 alkenyl group, a C_1-C_6 alkoxy group, a C_1-C_6 alkylthio group, a C_3-C_5 alkylene group, a C_2-C_4 alkylenoxy group, a C_1-C_3 alkylenedioxy group,

a phenyl group, a phenoxy group, a phenylthio group, a benzyl group, a benzyloxy group, a benzoylamino group, a C_2-C_7 alkanoyl group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 alkanoyloxy group, a C_2-C_7 alkanoylamino group, a C_2-C_7 *N*-alkylcarbamoyl group, a C_4-C_9 *N*-cycloalkylcarbamoyl group, a C_1-C_6 alkylsulfonyl group, a C_3-C_8 (alkoxycarbonyl)methyl group, a *N*-phenylcarbamoyl group, a piperidinocarbonyl group, a morpholinocarbonyl group, a 1-pyrrolidinylcarbonyl group, an amino group, a mono(C_1-C_6 alkyl)amino group, or a di(C_1-C_6 alkyl)amino group, wherein the substituent for the phenyl group, C_3-C_8 cycloalkyl group, aromatic heterocyclic group, or condensed ring is optionally substituted with one or more of a halogen atom, a hydroxy group, an amino group, a trifluoromethyl group, a C_1-C_6 alkyl group, or a C_1-C_6 alkoxy group;

R^2 is a hydrogen atom, a C_1-C_6 alkyl group, a C_2-C_7 alkoxycarbonyl group, a hydroxy group, or a phenyl group, in which the C_1-C_6 alkyl or phenyl group may be substituted with one or more of a halogen atom, a hydroxy group, a C_1-C_6 alkyl group, or a C_1-C_6 alkoxy group, and when $j = 0$, R^2 is not a hydroxy group;

j represents an integer of 0-2;

k represents an integer of 0-2;

m represents an integer of 2-4;

n represents 0 or 1;

R^3 is a hydrogen atom or a C_1-C_6 alkyl group optionally substituted with one or two phenyl groups each of which may be substituted with one or more of a halogen atom, a hydroxy group, a C_1-C_6 alkyl group, or a C_1-C_6 alkoxy group;

R^4 and R^5 are the same or different from each other and are a hydrogen atom, a hydroxy group, a phenyl group, or a C_1-C_6 alkyl group, in which the C_1-C_6 alkyl group is optionally substituted with one or more of a halogen atom, a hydroxy group, a cyano group, a nitro group, a carboxy group, a carbamoyl group, a mercapto group, a guanidino group, a C_3-C_8 cycloalkyl group, a C_1-C_6 alkoxy group, a C_1-C_6 alkylthio group, a phenyl group optionally substituted with one or more of a halogen atom, a hydroxy group, a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, or a benzyloxy group, a phenoxy group, a benzyloxy group, a benzyloxycarbonyl group, a C_2-C_7 alkanoyl group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 alkanoyloxy group, a C_2-C_7 alkanoylamino group, a C_2-C_7 *N*-alkylcarbamoyl group, a C_1-C_6 alkylsulfonyl group, an amino group, a mono(C_1-C_6 alkyl)amino group, a di(C_1-C_6 alkyl)amino group, or an aromatic heterocyclic group having 1-3 of heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof and optionally condensed with benzene ring, or R^4 and R^5 taken together form a 3 to 6 membered cyclic hydrocarbon;

p represents 0 or 1;

q represents 0 or 1;

G is a group represented by -CO-, $-SO_2-$, -CO-O-, $-NR^7-CO-$, $-CO-NR^7-$, -NH-CO-NH-, -NH-CS-NH-, $-NR^7-SO_2-$, $-SO_2-NR^7-$, -NH-CO-O-, or -O-CO-NH-, wherein R^7 is a hydrogen atom or a C_1-C_6 alkyl group, or R^7 taken together with R^5 represents C_2-C_5 alkylene group;

R^6 is a phenyl group, a C_3-C_8 cycloalkyl group, a C_3-C_8 cycloalkenyl group, a benzyl group, or an aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof, in which the phenyl, benzyl, or aromatic heterocyclic group may be condensed with a benzene ring or an aromatic heterocyclic group having 1-3 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom, a nitrogen atom, or a combination thereof, to form a condensed ring, and the phenyl group, C_3-C_8 cycloalkyl group, C_3-C_8 cycloalkenyl group, benzyl group, aromatic heterocyclic group, or condensed ring may be substituted with one or more of a halogen atom, a hydroxy group, a mercapto group, a cyano group, a nitro group, a thiocyanato group, a carboxy group, a carbamoyl group, a trifluoromethyl group, a C_1-C_6 alkyl group, a C_3-C_6 cycloalkyl group, a C_2-C_6 alkenyl group, a C_1-C_6 alkoxy group, a C_3-C_8 cycloalkyloxy group, a C_1-C_6 alkylthio group, a C_1-C_3 alkylenedioxy group, a phenyl group, a phenoxy group, a phenylamino group, a benzyl group, a benzoyl group, a phenylsulfinyl group, a phenylsulfonyl group, a 3-phenylureido group, a C_2-C_7 alkanoyl group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 alkanoyloxy group, a C_2-C_7 alkanoylamino group, a C_2-C_7 *N*-alkylcarbamoyl group, a C_1-C_6 alkylsulfonyl group, a phenylcarbamoyl group, a *N,N*-di(C_1-C_6 alkyl)sulfamoyl group, an amino group, a mono(C_1-C_6 alkyl)amino group, a di(C_1-C_6 alkyl)amino group, a benzylamino group, a C_2-C_7 (alkoxycarbonyl)amino group, a C_1-C_6 (alkylsulfonyl)amino group, or a bis(C_1-C_6 alkylsulfonyl)amino group, wherein the substituent for the phenyl group, C_3-C_8 cycloalkyl group, C_3-C_8 cycloalkenyl group, benzyl group, aromatic heterocyclic group, or condensed ring is optionally substituted with one or more of a halogen atom, a cyano group, a hydroxy group, an amino group, trifluoromethyl group, a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a C_1-C_6 alkylthio group, a mono(C_1-C_6 alkyl)amino group, or a di(C_1-C_6 alkyl)amino group.

17. A method of inhibiting the binding of a chemokine to the receptor of a target cell and/or its action on a target cell as set forth in claim 16, wherein k = 1 and m = 2 in the above formula (I).

18. A method of inhibiting the binding of a chemokine to the receptor of a target cell and/or its action on a target cell as set forth in claim 17, wherein $n = 0$ in the above formula (I).

19. A method of inhibiting the binding of a chemokine to the receptor of a target cell and/or its action on a target cell as set forth in claim 16, wherein $k = 0$, $m = 3$ and $n = 1$ in the above formula (I).

20. A method of inhibiting the binding of a chemokine to the receptor of a target cell and/or its action on a target cell as set forth in claim 16, wherein $k = 1$ and $m = 3$ in the above formula (I).

21. A method of inhibiting the binding of a chemokine to the receptor of a target cell and/or its action on a target cell as set forth in claim 16, wherein $k = 2$ and $m = 2$ in the above formula (I).

22. A method of inhibiting the binding of a chemokine to the receptor of a target cell and/or its action on a target cell as set forth in claim 21, wherein $n = 1$ in the above formula (I).

23. A method of inhibiting the binding of a chemokine to the receptor of a target cell and/or its action on a target cell as set forth in claim 16, wherein $k = 1$ and $m = 4$ in the above formula (I).

24. A method of inhibiting the binding of a chemokine to the receptor of a target cell and/or its action on a target cell as set forth in claim 16, wherein $j = 0$ in the above formula (I).

25. A method of inhibiting the binding of a chemokine to the receptor of a target cell and/or its action on a target cell as set forth in claim 16, wherein $p = 0$, $q = 0$ and G is a group represented by $-NR^7-CO-$ in the above formula (I).

26. A method of inhibiting the binding of a chemokine to the receptor of a target cell and/or its action on a target cell as set forth in claim 16, wherein R^2 is a hydrogen atom, R^3 is a hydrogen atom and R^7 is a hydrogen atom in the above formula (I).

27. A method of inhibiting the binding of a chemokine to the receptor of a target cell and/or its action on a target cell as set forth in Claim 16, wherein the substituent for the phenyl group, C_3-C_8 cycloalkyl group, aromatic heterocyclic group, or condensed ring in R^1 is one or more of a halogen atom, a hydroxy group, a C_1-C_6 alkyl group, a C_2-C_6 alkenyl group, a C_1-C_6 alkoxy group, a C_1-C_6 alkylthio group, a C_2-C_4 alkylenoxy group, a methylenedioxy group, a *N*-phenylcarbamoyl group, an amino group, a mono(C_1-C_6 alkyl)amino group, or a di(C_1-C_6 alkyl)amino group in the above formula (I).

28. A method of inhibiting the binding of a chemokine to the receptor of a target cell and/or its action on a target cell as set forth in claim 16, wherein the substituent for the phenyl group, C_3-C_8 cycloalkyl group, C_3-C_8 cycloalkenyl group, benzyl group, aromatic heterocyclic group, or condensed ring in R^6 is one or more of a halogen atom, a nitro group, a trifluoromethyl group, a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a phenylsulfonyl group, a C_2-C_7 alkanoylamino group, or an amino group in the above formula (I).

29. A method of inhibiting the binding of a chemokine to the receptor of a target cell and/or its action on a target cell as set forth in claim 16, wherein R^1 is a phenyl group or an isoxazolyl group in the above formula (I).

30. A method of inhibiting the binding of a chemokine to the receptor of a target cell and/or its action on a target cell as set forth in claim 16, wherein R^6 is a phenyl group, a furyl group, or a thienyl group in the above formula (I).

31. A method of inhibiting the binding of a chemokine to the receptor of a target cell and/or its action on a target cell as set forth in claim 16, wherein the chemokine is MIP-1α.

32. A method of inhibiting the binding of a chemokine to the receptor of a target cell and/or its action on a target cell as set forth in claim 16, wherein the chemokine is MCP-1.

33. A method of inhibiting the binding of a chemokine to the receptor of a target cell and/or its action on a target cell as set forth in claim 16, wherein

the chemokine receptor is CCR1.

34. A method of inhibiting the binding of a chemokine to the receptor of a target cell and/or its action on a target cell as set forth in claim 16, wherein the chemokine receptor is CCR2A or CCR2B.

35. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable C_1-C_6 alkyl addition salt as set forth in claim 1, wherein the compound is 4-[{N-(2-amino-5-chlorobenzoyl)glycyl}aminomethyl]-1-(4-chlorobenzyl)piperidine.

36. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable C_1-C_6 alkyl addition salt as set forth in claim 1, wherein the compound is 4-[{N-(2-amino-4,5-difluorobenzoyl)glycyl}aminomethyl]-1-(4-chlorobenzyl)piperidine.

37. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable C_1-C_6 alkyl addition salt as set forth in claim 1, wherein the compound is 4-[{N-(2-amino-5-trifluoromethylbenzoyl)glycyl}aminomethyl]-1-(4-chlorobenzyl)piperidine.

38. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable C_1-C_6 alkyl addition salt as set forth in claim 1, wherein the compound is 4-[{N-(2-amino-5-trifluoromethoxybenzoyl)glycyl}aminomethyl]-1-(4-chlorobenzyl)piperidine.

39. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable C_1-C_6 alkyl addition salt as set forth in claim 1, wherein the compound is 4-[{N-(2-amino-4,5-difluorobenzoyl)glycyl}aminomethyl]-1-(4-bromobenzyl)piperidine.

40. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable C_1-C_6 alkyl addition salt as set forth in claim 1, wherein the compound is 1-(2-amino-4-chlorobenzyl)-4-[{N-(2-amino-5-trifluoromethylbenzoyl)glycyl}aminomethyl]piperidine.

41. A compound, its pharmaceutically acceptable acid addition salt or its

pharmaceutically acceptable C_1-C_6 alkyl addition salt as set forth in claim 1, wherein the compound is 1-(3-amino-4-methoxybenzyl)-4-[{N-(2-amino-4,5-difluorobenzoyl)glycyl}aminomethyl]piperidine.

42. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable C_1-C_6 alkyl addition salt as set forth in claim 1, wherein the compound is 4-[{N-(2-amino-4,5-difluorobenzoyl)glycyl}aminomethyl]-1-{4-chloro-3-(methylamino)benzyl}piperidine.

43. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable C_1-C_6 alkyl addition salt as set forth in claim 1, wherein the compound is 4-[{N-(2-amino-5-trifluoromethylbenzoyl)glycyl}aminomethyl]-1-(2-thioxo-2,3-dihydro-1,3-benzoxazol-5-ylmethyl)piperidine.

44. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable C_1-C_6 alkyl addition salt as set forth in claim 1, wherein the compound is 3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-chlorobenzyl)pyrrolidine.

45. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable C_1-C_6 alkyl addition salt as set forth in claim 1, wherein the compound is 3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-methoxybenzyl)pyrrolidine.

46. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable C_1-C_6 alkyl addition salt as set forth in claim 1, wherein the compound is 3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(3,4-methylenedioxybenzyl)pyrrolidine.

47. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable C_1-C_6 alkyl addition salt as set forth in claim 1, wherein the compound is 3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(2,3-dihydro-1-benzofuran-5-ylmethyl)pyrrolidine.

48. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable C_1-C_6 alkyl addition salt as set forth in claim 1, wherein the compound is 3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-methylthiobenzyl)pyrrolidine.

49. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable C_1-C_6 alkyl addition salt as set forth in claim 1, wherein the compound is 3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-ethylbenzyl)pyrrolidine.

50. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable C_1-C_6 alkyl addition salt as set forth in claim 1, wherein the compound is 3-[{*N*-(2-amino-5-trifluoromethoxybenzoyl)glycyl}amino]-1-(4-ethylbenzyl)pyrrolidine.

51. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable C_1-C_6 alkyl addition salt as set forth in claim 1, wherein the compound is 1-(3-amino-4-methoxybenzyl)-3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]pyrrolidine.

52. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable C_1-C_6 alkyl addition salt as set forth in claim 1, wherein the compound is 3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(4-chloro-3-methylbenzyl)pyrrolidine.

53. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable C_1-C_6 alkyl addition salt as set forth in claim 1, wherein the compound is 3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-{4-hydroxy-3-(methylamino)benzyl}pyrrolidine.

54. A compound, its pharmaceutically acceptable acid addition salt or its pharmaceutically acceptable C_1-C_6 alkyl addition salt as set forth in claim 1, wherein the compound is 3-[{*N*-(2-amino-5-trifluoromethylbenzoyl)glycyl}amino]-1-(1,3-benzoxazol-5-

ylmethyl)pyrrolidine.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/23254

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D211/58 A61K31/435 A61K31/41 C07D207/14 C07D211/56 C07D211/26 C07D207/09 C07D401/12 C07D405/12 C07D409/12 C07D413/06 C07D413/14 C07D409/06 C07D405/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 217 286 A (OKAMOTO SHOSUKE ;SHOWA DENKO KK (JP)) 8 April 1987 see page 31, compound 42; claim 1 ---	1,3,6, 9-11,14
X	EP 0 417 698 A (HOECHST AG) 20 March 1991 see example 5C ---	1,3,6,9, 14,15

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 March 1999	25/03/1999
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer De Jong, B

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 107, no. 7, 17 August 1987 Columbus, Ohio, US; abstract no. 51382, KHALID, M. ET AL: "N,N'-disubstituted L-isoglutamines as novel cancer chemotherapeutic agent" XP002094911 see abstract & DRUGS EXP. CLIN. RES. (1987), 13(SUPPL. 1), 57-60 ;ISSN: 0378-6501,1987, ---	1,3,6, 9-11,14, 15
A	DATABASE WPI Section Ch, Week 9804 Derwent Publications Ltd., London, GB; Class B03, AN 98-035793 XP002094912 & JP 09 249566 A (TAKEDA CHEM IND LTD) , 22 September 1997 see abstract ---	1-54
P,X	WO 98 50534 A (SMITHKLINE BEECHAM CORP ;RU YU (US); VEBER DANIEL F (US); MARQUIS) 12 November 1998 see claim 1; examples -----	1-15

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.rnational application No.

PCT/US 98/23254

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 16-34
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 16-34 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

2. [X] Claims Nos.: not applicable
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claims Nos.: not applicable

In view of the extremely broad Markush claims 1-15, the search was executed with due regard to the PCT Search Guidelines (PCT/GL/2), C-III, paragraph 2.1, 2.3 read in onjunction with 3.7 and Rule 33.3 PCT, i.e. particular emphasis was put on the inventive concept, as illustrated by the examples. The international search was, in so far as possible and reasonable, complete in that it covered the entire subject-matter to which the claims are directed.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/US 98/23254

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
EP 0217286	A	08-04-1987	AU	598750	B	05-07-1990
			AU	6305186	A	02-04-1987
			CA	1297633	A	17-03-1992
			US	4895842	A	23-01-1990
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			JP	7053705	B	07-06-1995
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EP 0417698	A	20-03-1991	AT	135368	T	15-03-1996
			AU	639259	B	22-07-1993
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			DK	417698	T	22-07-1996
			ES	2086341	T	01-07-1996
			GR	3019331	T	30-06-1996
			JP	3106877	A	07-05-1991
			MX	9203284	A	31-07-1992
			NO	177143	B	18-04-1995
			PT	95278	A	22-05-1991
			US	5374731	A	20-12-1994
WO 9850534	A	12-11-1998	AU	7288598	A	27-11-1998